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Trends in in-hospital mortality, morbidity and interventions of very preterm infants in Switzerland.

A comparison of the years 1996, 2000 and 2004.

INAUGURAL-DISSERTATION
zur Erlangung der Doktorwürde der Medizinischen Fakultät
der Universität Zürich

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Zürich 2009

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1 Summary

Background: Very preterm birth is a major cause of mortality and morbidity for newborns and imposes a considerable burden on finite health care resources. Progresses in understanding of diseases and interventions, improvements in intensive care and some organisational changes like the centralisation of high-risk deliveries in perinatal centres leaded to a significant better outcome of very preterm infants in the last 30 years. Only few international publications analyse their short-term outcome on a nationwide basis, and for Switzerland no report on its temporal trend existed.

Objectives: The aim of this retrospective study was to analyse the in-hospital mortality rate, the incidence of major morbidities and the frequency of interventions for infants with less than 32 completed gestational weeks, inclusively a special focus on the gender. These results were compared with international publications. Furthermore, the temporal development of those variables was assessed for the years 1996, 2000 and 2004. Mathematical prediction models for the survivor and the short-term outcome were evaluated.

Methods: The Swiss Neonatal Network and Follow-Up Group prospectively collected perinatal data of infants born alive before 32 completed gestational weeks in Switzerland in 1996 (n=606), 2000 (n=674) and 2004 (n=654). The questionnaire contains 40 variables to obtain data on basic demographics, survivor and main morbidities during the first period of hospitalisation until discharge home. SPSS 12.0.1 is used to calculate the yearly rates and the average frequencies with their 95% confidence intervals and odds ratios, the Pearson Chi-squared respective Kaplan-Meier to assess the significance of a temporal trend. Multivariate linear regressions, a factor model and discriminant models are evaluated with the major variables.

Results: 18 (3.0%) infants died in the delivery room in 1996, 21 (3.1%) in 2000 and 24 (3.7%) in 2004. 573 children were admitted alive to a perinatal centre in 1996, 645 in 2000 and 630 in 2004. From the 1848 liveborns in the 9 perinatal centres, 47.5% were female and 74.6% were born by C-section. 23.0% of the liveborns were multiple births in 1996 and the rate increased significantly to 31.4% in 2004 ($p_C<0.01$). Also significant more infants were inborn over the period (94.3% in 2004 and 86.9% in 1996, respectively; $p_C<0.0001$).
The mortality rates didn't differ significantly over the years. The early neonatal mortality rate amounted to 8.3% (95% CI 7.1%-9.5%) and the late one to 3.5% (95% CI 2.6%-4.3%). 87.1% (95% CI 85.6%-88.6%) of the liveborns were discharged home. 50.3% of the infants with <26 completed gestational weeks died during their hospital stay (OR 8-15 versus older infants), 22.8% (OR 4.3-8.8 versus older infants) of the ones with 26-27 completed weeks. The mortality rate of the SGA infants was 23.4% (OR 1.7-3.5 versus AGA).
The incidence of those morbidities, which were highly associated with death, remained stable over time. The rate of intracranial haemorrhage grade 3-4 amounted to 7.9% (OR 9-19), the one of CLD was 31.5% (OR 3.4-24) and the one of BPD was 13.8% (OR 5-109). The incidence of survivors with a poor outcome, defined as intracranial haemorrhage grade 3-4, cystic periventricular leucomalacia ROP stage 3-4 or BPD was 18.5% (95% CI 16.6-20.4%) and remained stable over the years. The length of stay of the survivors tended to decrease from 67 days in 1996 (95% CI 65-70 days) to 65 days in 2004 (95% CI 62-67 days).
The rate of interventions increased significantly except major surgeries and mechanical ventilation. In 2004, antenatal steroids were given to 75.7% of the infants (64.2% in 2000, $p_C<0.0001$) and surfactant to 38.7% (30.0% in 1996, $p_C<0.01$). 80.5% of the children had respiratory assistance with CPAP (48.2% in 1996, $p_C<0.0001$). For the survivors, the duration of mechanical ventilation decreased from 8.6 days in 1996 to 6.9 days in 2004 ($p_C=0.07$), and opposite to that, the duration of CPAP treatment increased from 9.3 days in 1996 to 12.4 days in 2004 ($p_C=0.27$).

Conclusions: The higher frequency of interventions didn't affect the mortality and the incidence of major morbidities but was associated with a shorter length of stay.

2 Introduction

A national analysis of the mortality and morbidity of only very preterm infants – infants with less than 32 completed weeks – is published in different countries. There is none for Switzerland and this gap shall be closed with this study. It will be analysed if the incidence of mortality and major morbidities change in the period from birth to dismission home respectively death in the years 1996-2004 or if a trend can be found. One special focus is the in-hospital poor outcome, defined as survival with intracranial haemorrhage grade 3 or 4, cystic periventricular leucomalacia, ROP stage 3 or 4 and/or bronchopulmonary dysplasia. The years 1996, 2000 and 2004 are taken because The Swiss Neonatal Network and Follow-up Group set up special forces to ensure that data of these years are complete and correct.

Some therapies, interventions and the duration of hospitalisation were collected as well. Their temporal changes will be analysed as well as their influence on the mortality and the morbidities.

Subsequently, the results are compared with studies of different European countries, North America and the Pacific region. The aim is to find out if the mortality rate and the incidence of the morbidities are significantly different between Switzerland and single foreign countries.

At the end, some mathematical models are constructed that serve as prediction especially for an in-hospital outcome of the very preterm infants. The quality of the models is analysed as well.

3 Methods

3.1 Swiss Society of Neonatology and the Minimal Neonatal Data Set

The Swiss Neonatology Group meets regularly since years and it founded the Swiss Society of Neonatology (NEO) in 1995 with the goal to improve the quality of neonatal care. In the same year, NEO inaugurated the Swiss Neonatal Network & Follow-Up Group as a non-profit voluntary collaboration of health care professionals. Today, the Network is comprised of all nine Neonatal Intensive Care Units (NICUs), most of the smaller Neonatal Units (NUs) and most Neuropediatric Centres in Switzerland under the auspices of the Swiss Society of Neonatology. Further information can be found on its internet page www.neonet.ch.
The Network maintains the database Minimal Neonatal Data Set (MNDS) including information about the demographics and outcome of high-risk newborn infants. The Minimal Neonatal Dataset collects a standardized, anonymised data set of every child born at a participating hospital or transferred to a participating hospital from another hospital without intermediate discharge home. The data is submitted electronically or by paper form to the Network and is used to provide comprehensive, confidential reports for participating hospitals. These reports serve as the foundation for local quality improvement projects, internal audits and outcome research.

3.1.1 Registration criteria

The MNDS contains all liveborn infants between 400g and 1499g birth weights (VLBW) or between $23^0/_7$ and $31^6/_7$ gestational weeks (very preterm). A textbook definition of liveborns includes all infants with at least one of the vital sign heart beat, umbilical cord pulsation or breathing [28]. A practical definition includes all infants with a real chance for surviving. Difficulties arise from the different handling of its definition in the centres. A still birth has no vital signs and a birth weight of over 1000g and they aren't included in the MNDS.

3.1.2 Data collection and verification

Data are collected in the hospitals by filling out the specific MNDS form. They are transferred to the Network by paper form or electronically and stored in a filemaker database at the University hospital of Zurich. Only anonymised data are collected and stored. The aim of a protocol, established in 2003, is to encompass approximately 95% of all preterm births. A scientific committee supervises the data collection and evaluation. The data verification is performed by identifying missing or erroneous data, which are corrected by contacting the responsible hospital.
Two data records had to be excluded because they didn't fulfil the registration criteria of gestational age or birth weight. A third one in 2000 was twice in the database and was deleted. 2239 infants fulfilled the registration criteria: 720 in 1996, 773 in 2000 and 746 in 2004.

3.1.3 Data set variables

In this paragraph, only the variables that are used for the analysis are described in detail.

3.1.3.1 Gestational age

The gestational age is equivalent to the weeks and days in utero calculated from the first day of the last normal menstruation. It is assessed by last menstrual period and first trimester ultrasound.

3.1.3.2 Birth weight

The birth weight is the first weight of the newborn within the first hours of live after birth. It wasn't provided for one (0.1%) infant in1996.

A child is light or small for gestational age (SGA) if its birth weight is $<10^{th}$ percentile of the population specific birth weight curve. A child is heavy or large for gestational age (LGA) if its birth weight is $\geq 90^{th}$ percentile of the same birth weight curve. The children who are neither SGA nor LGA, i.e. whose weight is $\geq 10^{th}$ and $<90^{th}$ percentile, are appropriate for gestational age (AGA). The population specific birth weight curve is based on German infants[1].

3.1.3.3 Head circumference

The head circumference is the longest occipito-frontal circumference in millimetre. The head circumference wasn't collected in 1996 except for one infant. There were 44 (5.7%) missing values in 2000 and 16 (2.1%) in 2004.

Small (SHC), appropriate (AHC) and large (LHC) head circumference is defined analogously to SGA ($<10^{th}$ percentile), AGA and LGA ($\geq 90^{th}$ percentile) with the population specific head circumference curve[2]. Subnormal head circumference is associated with a poorer intelligence quotient equivalent, perceptual motor skills, academic achievement and adaptive behaviour [55].

3.1.3.4 The pH-value of the umbilical artery

The pH-value of the umbilical artery wasn't collected in 1996 at all. Values above 7.50 were assumed to be wrong and were defined as missing value – one infant had a ph-value 7.76 in 2004. There were 109 (14.1%) missing values in 2000 and 70 (9.4%) in 2004.

3.1.3.5 APGAR score

There are no consistent data on the significance of the APGAR score in preterm infants and it is known that the score has limitations. For VLBW infants, the CRIB score is more validated [53], however it will not be used here because of its lack of reliability in the examined years. For infants with ≥ 26 completed weeks, the APGAR scores after 1 and 5 minutes are good predictors of mortality[3] [25]. Casey showed that the prediction of outcome is improved by combining the score with the pH-value of the umbilical artery [9]. For infants with 25 completed weeks, all three APGAR scores predict well the survival at 180 days without severe brain damage and its prediction can be improved by combining the APGAR score with the CRIB score [71]. The APGAR score can't discriminate between normal and disabled survivors[4] [83].

The APGAR score wasn't collected in 1996 either. For the APGAR score after one minute, 14 (1.8%) entries were missing in 2000 and 8 (1.1%) in 2004. For the one after five minutes, 12 (1.6%) infants didn't have the information in 2000 and 9 (1.2%) in 2004. 16 (2.1%) children didn't have an APGAR score after ten minutes in 2000 and 11 (1.5%) in 2004.

3.1.3.6 Centre

The MNDS take account of infants who are born in one of the nine perinatal centres and their peripheral perinatal hospitals. In 2004, only the nine perinatal centres are included.

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[1] The birth weight of German newborns corresponded with the one of Swiss infants only for early gestational ages. The German children were heavier than the Swiss ones. The gap got bigger with increasing gestational age [84]. The difference is small for very preterm infants and therefore there will be a negligible error by using the German percentile curves. Here the German percentile curves are used, based on the infants born in 1992 [1, 16].

[2] See footnote 1.

[3] The study couldn't support the grouping of infants at risk in Apgar score groups with a cut-off score 4 and 7.

[4] The Bayley scale of Infant Development was used in a study of infants below 1000g at the age of 2 years.

3.1.3.7 Gender

No missing values.

3.1.3.8 Singleton and multiple birth

The average gestational duration decreases and the risk of a premature birth increases with the number of infants in the uterus [50]. Reasons for earlier birth of multiple children can be due to mechanic stress of the lower uterine segment, higher volume of the amniotic fluid or other multifactors.

3.1.3.9 Birth location

The category "inborn infants" should include all infants born in a neonatal centre. Analogously, the outborn infants should be born outside a neonatal centre. However in MNDS, the inborns are defined as born in the centre and the outborns are defined as born outside the centre. 2 (0.3%) entries were missing in 2000.

3.1.3.10 Mode of delivery

Arpino showed for very preterm Italian infants that the C-section had no effect on cerebral ultrasonography abnormalities and that the mortality rate wasn't reduced [66].
MNDS distinguish between five modes of delivery. For the analysis, they are grouped to Caesarean section (C-section) and vaginal delivery. Vaginal delivery includes cephalic spontaneous, forceps or ventouse and breech spontaneous or assisted. 14 (1.8%) data entries were missing in 2000 and 3 (0.4%) in 2004.

3.1.3.11 Death in delivery room

The information if the infant died in the delivery room wasn't provided regularly by all the centres in the three observed years. It can't be ruled out that a child whose birth and death date is on the same day died in the delivery room. Missing entries were defined as no death in delivery room.

3.1.3.12 Congenital malformation

Morphological development disorders can be detected with echograph between the 11^{th} and 14^{th} gestational week [50]. A malformation of the heart is the most frequent congenital malformation.
The MNDS distinguish between minor and major malformations. A major one is lethal or need specific diagnostic or therapeutic interventions during the neonatal period i.e. till the 28^{th} day of live. The children with minor malformations are grouped together with the ones without any malformations. For a listing of the major malformations, see www.euronet.org. The records with no information about congenital malformation - 14 (0.6%) records, we assumed to have no malformation.

3.1.3.13 Persistent ductus arteriosus (PDA)

PDA is the most frequent cause for early born to have a left-right shunt and lung oedema [28]. The use of a near-infrared spectroscopy (NIRS) is a new screening tool that is discussed in the literature [80]. An ongoing debate is about whether or not to treat a PDA because of a high rate of its spontaneous closure during the first two years [69].
In MNDS, the definition includes only the symptomatic cases requiring indomethacin or a surgery and, if possible, that are confirmed by echocardiography. Infants with missing value -11 (1.4%) in 2000, 5 (0.7%) in 2004 - were assumed to have an absent PDA.

3.1.3.14 Sepsis

Early-onset sepsis – defined as sepsis within first week of life – is often fulminant and multi systemic, late-onset infections – defined as sepsis within a hospitalisation stay – represent the risk of invasive lines, life-saving treatments and the immaturity of the immune system [72]. The reduced functional response to bacterial cell wall components appears to be part of the functional immaturity [¨77]. An Isreali study showed that the use of tocolytics and low gestational age are independent risk factors for early neonatal sepsis [60].

A sepsis is proven if a child has clear clinical, radiological or histological evidence of an infection and at least on microbiologically relevant positive blood culture. For the analysis, the infants were categorised into two groups: (a) absent or suspected sepsis, (b) proven sepsis. The 5 (0.7%) missing entries in 2004 were defined as an absent sepsis.

3.1.3.15 Necrotising enterocolitis (NEC)

Necrotising enterocolitis (NEC) is an acute haemorrhagic-necrotising inflammation in the intestine tract of unknown origin with a complex and multifactor pathogenesis. Enteral alimentation and prematurity are the only consistent epidemiological precursors. Currently, there are no biomarkers of the risk and the severity of this disease [81, 52].

It is the most frequent cause for an acute abdomen and lethal disease of the gastrointestinal tract of very early born children [22]. It is associated with a high mortality, especially for small children [28].

The incidence can be significantly lowered by the application of steroids for the maturation of the lung and antibiotics [50]. Contrarily, Pietz argues, that the late-onset, slow and continuous drip feeding and the avoidance of indomethacin and early dexamethasone treatment contribute to the prevention of NEC [75].

A NEC is proven if a child has clinical signs and intramural gas confirmed by X-ray or at laparatomy. For the analysis, the infants were categorised into two groups: (a) absent or suspected NEC, (b) proven NEC. The 5 (0.7%) missing entries in 2004 were defined as an absent NEC.

3.1.3.16 Retinopathia praematurum (ROP)

Retinopathia praematurum (ROP) is a multifactor caused vasoproliverative disease of the retina. Only early born children, especially if treated with oxygen can go down with the disease because they have incomplete vascular retinas with a peripheral avascular zone whose seize is determined by the gestational age. There are two phases of progress: The first one begins with delayed retinal vascular growth and partial regression of existing vessels after birth till approximately 30-32 postmenstrual weeks. The second one includes a hypoxia-induced pathological retinal neovascularisation. The new vessels sprout into the vitreous gel and lens and can cause retinal detachment [68].

The gestational age is an obvious risk factor. Others that are still in discussion or had contradictory results are vitamin E and elevated glucose [68]. International guidelines for routine screening are controversial. Lee [8] argues that a screening of infants with birth weight less than 1201g only is a most cost-effective strategy.

In Switzerland, ophthalmic examination is recommended for all infants with birth weight <1500g or gestational age <32 weeks at 6-7 postnatal weeks. Therefore only the survivors of perinatal centres are included in the following analysis - 502 infants in 1996, 550 in 2000 and 558 in 2004, overall 1610 children. MNDS take account of ROP in both eyes separately. For the analysis, the stage was defined as worst stage in one eye.

3.1.3.17 Respiratory distress

A respiratory distress syndrome/Hyaline membrane disease (RDS) is the most frequent reason for death in the neonatal period [28] and the most frequent cause for morbidity in premature infant [72]. It is grouped by X-ray in four stages. RDS is one of the complications of the organ immaturity and it is

caused by the lack of surfactant [50]. A subsequent lung disease with severe RDS characterizes chronic lung disease respective bronchopulmonary dysplasia (see next subchapter).
Early surfactant administration to infants with RDS requiring assisted ventilation leads to decreased risk of acute pulmonary injury and reduces neonatal mortality or CLD. The two strategies are rescue therapy – treatment of established disease – and prophylaxis – immediate administration after birth to infants at high risk. For the latter, Fiori argued that the stable microbubble test[5] (SMT) can be used for the candidate selection in less than 30 minutes after birth.
In MNDS, the definition includes all infants with at least two of the following symptoms, recorded twice 15-30 minutes apart: respiratory rate > 60/min, cyanosis in room air, inspiratory retractions, expiratory grunting and nasal flaring. Excluded are all infants if the symptoms have been lasting less than three hours or the infant has been intubated immediately after birth for prolonged apnoea without respiratory effort. No data entries were missing. For the analysis, respiratory distress includes the Hyaline membrane disease and the pneumopathy with other or unknown causes.

3.1.3.18 Chronic lung disease (CLD) and Bronchopulmonary dysplasia (BPD)

There are two different ways in the literature to define a chronic lung disease[6]: (a) a requirement for supplemental oxygen at day 28; (b) a requirement for supplemental oxygen at 36 weeks' postmenstrual age (PMA). The first definition is named as a CLD, the second as BPD. No data entries were missing.
An acute neonatal lung disease is characterized by a severely reduced functional residual capacity (FRC). In infants with CLD, FRC may remain reduced due to hyperinflation with or without gas trapping and secondary to airway obstruction [78].
The long-term complication of CLD is an increased risk for respiratory infections and an increased evidence of bronchial hyperreactivity in the first year of live. At school age, the infants with CLD didn't show any difference in respiratory symptomatology and had an almost normal lung function with a higher risk of reversible small airways obstruction compared to a control group of preterm infants [74].
Bronchopulmonary dysplasia (BPD) is a major cause of increase length of hospitalisation among VLBW infants [51]. The reason is that almost no effective preventive[7] and therapeutic intervention is available, also because the molecular mechanism of the pathogenesis is not well understood. Rehan could show that the alveolar Parathyroid Hormone-related Protein (PTHrP) signalling path is involved and this might be a future approach to an intervention [57]. A new hypothesis uses environmental effects and genetic factors for the existence of BPD whereby candidate genes are surfactant apoprotein and inflammatory genes [54].
Vrijlandt [82] could show that preterm birth affects respiratory health at 3-5 years of age. The infants didn't have more respiratory symptoms than the preterm ones without BPD, but they had lung function abnormalities (lower mean reactance, higher resonance frequency).

[5] The test bases on the forming of microbubbles by surfactant containing solutions when agitated through a Pasteur pipette. Very small samples of amniotic, tracheal or gastric fluid can be used for this test [48].
[6] The National Institute of Child Health and Human Development/National Heart, Lung and Blood Institute proposed a severity-based definition of BPD at a workshop in 2000 for very preterm infants:

- Mild BPD: need for supplemental oxygen (O_2) for ≥28 days, but not at 36 weeks' PMA or discharge,
- Moderate BPD: O_2 for ≥28 days plus treatment <30% O_2 at 36 weeks' PMA,
- Severe BPD: O_2 for ≥28 days plus ≥30% O_2 and/or positive pressure at 36 weeks' PMA.

Ehrenkranz argued that this definition would identify more accurately a spectrum of risk for adverse pulmonary and neurodevelopmental outcomes in early infancy [30].
[7] Intramuscular vitamin A is an effective and safe preventive treatment for BPD. Inositol and CPAP might be other effective preventions [63].

3.1.3.19 Cerebral ultrasonography

For the MNDS, cerebral ultrasound examination is recommended for all infants with birth weight <1500g or gestational age <32 weeks. The cerebral ultrasonography should be performed within the first 24 hours, at day 3 and 7 and then every one or two weeks until final discharge.
The hospitals reported if the infant wasn't examined or if the cerebral ultrasound examination was normal or abnormal.

3.1.3.20 Intracranial haemorrhage

The fragile capillary and arterial system of the subependymal germ layer often lead to the complication [28]. Fluctuation in arterial blood pressure leads to variations in cerebral blood flow due to the immature cerebral blood flow autoregulation [59]. The majorities of haemorrhages are grades 1 and 2 (Papile classification) and these are usually asymptomatic [49]. The prognosis for mental deficits and motoric disturbances is bad especially for grade 3 and 4. The incidence of intraventricular haemorrhage (IVH) include among other things can be reduced by preventing perinatal infections or by applicating steroids to induce the maturation of the lungs [50]. The exact day of bleeding remains controversial, most studies agree that it doesn't usually occur immediately after birth[8] but within 1 to 2 days of delivery. Factors that are associated with a higher incidence include hypoxia, blood transfusion, blood replacement and the need of mechanical ventilation [49]. The plasma level of activin A was higher at birth for preterm infants who developed later an IVH and this is maybe useful for the identification of infants at high risk for IVH [46]. PVL and hydrocephalus are complications of intracranial haemorrhage [49].
The infants were categorised for the analysis into five groups: (a) no intracranial haemorrhage, (b) subependymal haemorrhage (Classification of Papile grade 1), (c) intraventicular haemorrhage (IVH) without distention (grade 2), (d) IVH with distention (grade 3), (e) intraparenchymatous with or without intraventricular haemorrhage (grade 4). Analysing the 609 (27.2%) missing values - 1 in 2000, 608 in 2004: 497 infants had a normal examination finding and were defined as no intracranial haemorrhage, 82 children had an abnormal cerebral ultrasound finding and were defined as missing value and 30 infants didn't have a cerebral ultrasonography and were defined as missing value as well. At last, there are 112 (5.0%) infants with no information about the incidence of an intracranial haemorrhage.

3.1.3.21 Ventricular dilatation

The neurodevelopmental outcome of very preterm infants who had additionally an IVH had a significant lower performance IQ – measured by Test of Motor Impairment, the test of Visuo-Motor Integration and the Wechsler Intelligence Scales for children - at age 8 years than the ones with a normal ultrasound examination. The children with only a ventricular dilatation didn't differ significantly from the latter [64].
The infants were categorised for the analysis into two groups: (a) no ventricular dilatation, (b) ventricular index above 97th percentile. Analysing the 720 (32.2%) missing values - 2 in 2000, 718 in 2004: 498 had a normal examination finding and were defined as no ventricular dilatation, 191 had an abnormal cerebral ultrasound finding and were defined as missing value and 30 infants didn't have a cerebral ultrasonography and were defined as missing value as well. The infant with a missing value had a holoprosencephaly and it was defined as >4mm above 97th percentile. Filling up the entries, still 221 (9.9%) infants had no information about ventricular dilatation.
The infants with a ventricular index above 97th percentile were categorised for an additional analysis again into two groups: (a) with intracranial haemorrhage, (b) no intracranial haemorrhage. 7 infants

[8] Other authors estimate that 25-75% of the IVH in the first few days of life occur within 6-12 hours of delivery in the period of the greatest physiological instability [59].

who had an information about ventricular dilatation had none about intracranial haemorrhage and were defined as missing value, in total 228 (10.2%) missing values.

3.1.3.22 Periventricular leucomalacia (PVL)

The neuronal stem cells are formed in the germinal matrix zone during the embroynal and fetal period. Afterwards they migrate radially to the surface of the cortex through the white substance. The metabolic activity diminuishes with the maturity of the brain. There is an involution on the verge from preterm to term birth and the haemodynamic borderline territories of the brain shift. If the periventricular white matter is damaged, a periventricular leucomalacia (PVL) develops [62]. It mainly affects preterm infants and causes severe neurological damage - e.g. infantile cerebral parese. The diagnosis should be done by cranial ultrasonography on infants at risk because almost 50% of the infants with cystic PVL didn't show neurologic abnormalities at discharge [5]. In PVL, immunocytochemical markers of liped peroxidation and protein nitration are significantly increased [47].

The infants were categorised for the analysis into three groups: (a) no leucomalacia, (b) echogenic leucomalacia, (c) cystic with or without echogenic leucomalacia. Echogenic PVL is defined in the MNDS as a periventricular hyperechogenicity lasting for more than 14 days and if infants die before day 14, anoxic-ischemic encephalopathy diagnosed at an autopsy is equivalent. Cystic PVL is defined as one or several cysts in the white matter of the brain. Analysing the 653 (29.2%) missing values - 3 in 2000, 650 in 2004: 497 infants had a normal examination finding and were defined as no ventricular dilatation, 126 children had an abnormal cerebral ultrasound finding and were defined as missing value and 30 infants didn't have a cerebral ultrasonography and were defined as missing value as well. At last, there are 156 (7.0%) infants with no information about the incidence of a periventricular leucomalacia.

3.1.3.23 Neonatal outcome

The neonatal outcome is separated in three categories: (a) all infants who died during their stay in a hospital, (b) a poor neonatal outcome and (c) a good neonatal outcome. A poor neonatal outcome includes all survivors who had at least one of the following diagnosis: (a) intracranial haemorrhage grade 3 or 4; (b) cystic periventricular leucomalacia; (c) ROP stage 3 or 4; (d) bronchopulmonary dysplasia.

3.1.3.24 Length of stay (LOS)

The length of stay (LOS) involves the period from the date of birth till the discharge home respectively the date of death. This information couldn't be calculated for 166 - 11 (1.5%) in 1996, 45 (5.8%) in 2000 and 110 (14.7%) in 2004 - children because only the first discharge to a second hospital was provided however not the final discharge home.

With the available discharge dates, 19 survivors had a calculated less than 34 completed gestational weeks at dismission. Children of that age weren't mature enough to be released. It seems more likely that the children were older than the calculated age by ultrasound. The length of stay was defined as missing values for those infants.

3.1.3.25 Antenatal steroids

The labour should be prolonged for at least 48 hours at less than 33 completed gestational weeks in order to induce the maturation of the lungs with antenatal steroids. The physiological maturation of lungs ends approximately in the 34^{th} gestational week. With the application of antenatal steroids, the chance of surviving rise for 5% per day in the 25^{th} gestational week and for 1% per day in the 28^{th} gestational week [50]. Antenatal steroids should be given to any women at risk of preterm delivery

before 34 weeks gestation[9] [67, 84]. On the other hand, Cavalieri [42] argues that due to the long-term effect of antenatal steroids on the health they should only be applied if a very high risk of preterm birth exists and the likelihood of severe respiratory distress syndrome is substantial. Other advantages of the twice given doses of Beclamethasone are the reduced incidence of infant respiratory distress syndrome, intracranial haemorrhage, NEC and a reduction of the neonatal mortality rate [84].
In the MNDS, an infant is said to have prenatal steroids if an appropriate dose was given. That means, at least two doses with the first dose more than 24 hours and the last dose less than 14 days before birth. This information wasn't collected in 1996. If the information isn't known, the variable is set to no steroid application. For the analysis, the incomplete and complete application of steroids is grouped together.

3.1.3.26 Surfactant treatment

No missing values.

3.1.3.27 Mechanical ventilation

198 (8.8%) missing values were defined as no ventilation.

3.1.3.28 Continuous positive airways pressure (CPAP) treatment

91 (4.1%) infants with missing values were defined as ones with no CPAP treatment.

3.1.3.29 Surgery

6 (0.3%) missing values were defined as no surgery.

3.1.4 Data completeness: comparison with the Swiss Federal Statistical Office

7.2 million persons lived permanently in Switzerland in 2000, increasing by about 200'000 all five years [33]. Like in almost every European country, Switzerland has a decreasing excess of birth over deaths since at least 1950. It decreased from 8 in 1950 to 1.2 per 1000 inhabitants in 2003.
The Swiss Federal Statistical Office (BfS) registered 78'458 liveborns in 2000, which means 10.9 per 1000 inhabitants. The number of births decreased from 83'007 in 1996 to 73'082 in 2004 (less than 1%). The amount of the VLBW infants (infants with less than 1500g), increased from 7.6‰ to 9.0‰ of total births between 1996 and 2004.
In the examined years, the Swiss Federal Statistical Office only collected the information on the birth weight, not the gestational age. In order to assess the completeness of the MNDS, the number of infants with birth weight <1500g, included in MNDS, are therefore compared with the data set of the BfS (Table 1 left). It is obvious that the willingness of the centres to deliver their data to MNDS, increased over time to 93% in 2004.

[9] Betamethasone for two courses, 2 weeks apart. Dexamethasone should be avoided in preterm infants because of its effects on cognitive function, psychiatric-related behaviour and other aspects of neurological development; other steroids should not be given either.

Table 1: Number of live born infants with birth weight <1500g and 400 - 1499g respectively registered in MNDS and Swiss Federal Statistical Office (BfS)

Birth weight <1500g	BfS	all centres in MNDS		9 centres in MNDS	
	n	n	% of BfS	n	% of BfS
1996	632	556	88.0%	543	85.9%
2000	695	613	88.2%	603	86.8%
2004	630	585	92.9%	585	92.9%
All infants	1957	1754	89.6%	1731	88.5%

Birth weight 400-1499g	BfS	all centres in MNDS		9 centres in MNDS	
	n	n	% of BfS	n	% of BfS
1996	625	556	89.0%	543	86.9%
2000	653	610	93.4%	600	92.0%
2004	613	582	94.9%	582	94.9%
All infants	1891	1748	92.4%	1725	91.2%

A difference between the two data sets can partially be explained by the different definition of live born. The Federal Statistical Office included all infants who are registered by their parents as liveborns in the birth registry. Therefore there could be a difference in infants with birth weight <400g. If only the number of infants with birth weight between 400g and 1499g are included in the comparison, MNDS reaches a higher percentage of completeness (Table 1 right), 95% in 2004.
A higher completeness of the MNDS over time can also be explained by a tendency of centralisation in Switzerland, which means the VLBW infants were born more likely in perinatal centres than in their affiliate peripheral centres. This is supported by a change in the MNDS data collection done in 2004 when only the data of the nine perinatal centres were included in the data set.

3.1.5 The subsets of the MNDS data set

Due to the inclusion criteria of the infants, the MNDS data set can be splitted into two data subsets: (a) one data set containing only the infants with gestation age < 32 completed weeks (very preterm) and (b) one data set including the infants with birth weight < 1500g (VLBW). The distribution of the set of VLBW infants has a lower median of gestation age and birth weight compared to the set of very preterm infants and the complete MNDS data set (Table 2). Assuming that birth weight and especially gestation age is important for the outcome of an infant, it doesn't surprise that the mortality rate is lower and the percentage of a good neonatal outcome of this subset is higher than the one of the two other data sets. VLWB infants has a significant higher mortality rate (p_C[10]=0.014; OR=1.24, 95% CI 1.04-1.47) and a significant lower poor outcome (p_C=0.004; OR=1.22, 95% CI 1.07-1.40) than all infants of the MNDS. Very preterm infants has only a significant higher poor neonatal outcome (p_C=0.034; OR=1.15, 95% CI 1.01-1.32) than all infants of MNDS. The mortality rate and the good neonatal outcome of both MNDS data subsets don't differ significantly.

Table 2: Comparison of the complete MNDS data set with its subsets: infants with gestational age <32 completed gestational weeks and infants with birth weight <1500g

		GA <32 weeks	BW <1500g	MNDS
Nu of observation (n)		1934	1754	2239
GA	Min.	$23^2/_7$	$23^2/_7$	$23^2/_7$
	Median	$29^3/_7$	$29^0/_7$	$30^0/_7$
	Max.	$31^6/_7$	$39^5/_7$	$39^5/_7$
BW	Min.	370	370	370
	Median	1190	1110	1220
	Max.	2750	1499	2750
Mortality rate		15.7%	16.9%[1]	14.1%
Good neonatal outcome		68.8%[1]	67.5%[2]	71.8%

Note: subsets versus complete MNDS data set
[1]: p_C<0.05
[2]: p_C <0.01

[10] Pearson Chi-square p-value (p_C), the odds ratio (OR) and 95% confidence interval (CI)

The gestational age is considered to be a better predictor of the outcome for very preterm infants than the birth weight and is more useful to make decisions before birth [2, 19]. In the following chapters, the analysis is therefore done only for the very preterm infants if nothing else is indicated. The tables are listed in the appendix.

3.2 Statistical methods

SPSS Release 12.0.1 is used for the statistical calculations. The chi-square test compares the independence of two or more unrelated samples. The two variables are assumed to be independent if the observed frequencies of the rows of the cross table are the same as the expected frequencies. To use the test, less than 20% of the fields should have a frequency of less than five and the sums of the rows and columns should be greater than zero; if this requirement isn't fulfilled, the exact test of Fischer has to be applied. The two variables are independent, if the result is $p<0.05$. A standardised residuum of greater or equal two shows a significant difference between the observed frequencies of cases with the expected ones. It should be noted that a statistical coherence doesn't allow any conclusions on causality. There are several tests to compare the mean value of two independent variables. If the variables are normally distributed, the t-test is applicable.

The (multiple) linear regression is used to explain a dependent variable with one respective a set of independent variables. The quality of the regression is assessed with the adjusted R^2, F-statistic (with 95% quantile) and the standard error of the estimate. The t-value is calculated to asses the significance (95% quantile) of the coefficients of the regression and to get their 95% confidence intervals (CI). The normal assumptions are made to use the regression: (a) a correct specification of the linear model, (b) a zero expected value and a constant variance (homoscedasticity) of the error terms, (c) no correlation between the independent variables and the error terms, (d) no linear dependency between the independent variables (no perfect multicollinearity). The best linear unbiased estimator can be calculated with these assumptions. The calculation of the significance tests uses the further assumption of normal distributed error terms.
Reasons for a lack of fit are through the existence of outliers in the data or the misspecification of the model [35]. The transformation of the explanatory variables can improve the model. If the error distribution and the functional form of the relationship are unknown, a transformation should gain a compromise between [35] (a) constant error variance, (b) approximately normal errors, (c) additivity, (d) a linear relationship between the response variables and the explanatory variables and (e) straightforward scientific interpretation.

The aim of the factor analysis is to sort out the independent factors of a set of variables. The quality of the procedure depends on the selected variables, which are relevant for the examined question. The correlation matrix of the selected variables reveals if any of the variables have a common attribute such that some of the variables can be excluded; this can be assessed by the calculation of the significant levels, the inverse of the correlation matrix, the anti-image-covariance-matrix[11] or by using the Kaiser-Meyer-Olkin-criteria[12].
The next step estimates the communalities to express the amount of the variance explained by all the factors. The sum of all communalities is usually less than one because the factors can't explain the total variance and there is still an error of measure or other factors. The more variables are used, the

[11] The image corresponds to the amount of variance that is explained by the other variables in the context of a multiple regression analysis and the anti-image corresponds to the one that is independent of the other variables. The correlation matrix can't be used for the factor analysis if the number of non-diagonal elements of the anti-image-covariance matrix with a value > 0.09 don't exceed 25% (criteria of Dziuban and Shirkey).
[12] A correlation matrix with a measure of sampling adequacy (MSA) less than 0.5 can't be used for the factor analysis. The MSA should be ≥0.8 – MSA ≥0.9 marvellous; ≥0.8 meritorious; ≥0.7 middling; ≥0.6 mediocre; ≥0.5 miserable; ≥0 unacceptable. This criterion is said in the literature to be the best procedure to test the correlation matrix.

less important are the communalities. There are two methods now: principal component and principal axis analysis. The aim of the first method is to reproduce the data structure with factors as less as possible. The latter wants to explain the variance of the variables with factors and the correlations are interpreted causally. The principal axis factoring[13] or the principal component analysis[14] is used to extract the factors.
The number of factors is selected by the Kaiser criteria[15] and/or the Scree-test[16]. For the interpretation of the factors, it may be useful to rotate the factors without loosing any power of explanation. The Varimax rotation uses an orthogonal rotation.
The principle of Parsimony (Occam's Razor) is the reason to use the factor analysis [35]: the correct explanation is the simplest explanation i.e. (a) models should have parameters as less as possible, (b) linear models should be preferred to non-linear models, (c) experiments relying on few assumptions should be preferred to those relying on many, (d) models should be pared down until they are minimal adequate and (e) simple explanations should be preferred to complex explanations.
Using the factor analysis, you should bear in mind that categorical data (e.g. gender, mode of delivery etc) are generally not suitable for factor analysis. However data for which Pearson correlation coefficients can sensibly be calculated should be suitable for factor analysis.

The discriminant analysis is used for testing if two or more groups differ significantly. If two groups have more than one attribute, the variance analysis can be used.
In the case of two existing groups, the discriminant function and the linear regression function are equivalent in the sense that both equations have a different standardization.
In the case of more than two groups, min(G-1,J) different discriminant functions are constructed and all of them are orthogonal respectively uncorrelated, where G is the number of groups and J is the number of attributes. Usually G<J and if not, G should be reduced. The amount of eigenvalue (explained amount of variance) EA_k of the k-th discriminant function quantifies the amount of how much of the total variance the variance of the discriminant function explains. The total variance is explained by all discriminant functions (for two groups holds $EA_k/(1+ EA_k)=R^2$). The sum of all EA_k is equal 1.
The Wilks'Lambda/U-statistic[17] is used as criterion for testing the discriminant and it is equal to the non-explained variance as percentage of the total variance. The smaller the Wilks'Lambda value is the better the selectivity of the discriminant function will be. The Wilks'Lambda can be transformed into a significance test. For several discriminant function, all Wilks'Lambda are multiplied (multivariate Wilks'Lambda) to test the difference between the groups and there is also a significance test for the discriminant function.
A classification function can be constructed without using the discriminant function. The assumption is that the groups have the same variance which is tested by the Box's M- and F-value. This function allows including a priori possibilities that a child belongs to one group. In order to use this procedure, no element of the sample (i.e. child) should belong to more than one group.

[13] Squared multiple correlation coefficients are placed in the diagonal of the correlation matrix as initial estimates of the communalities. These factor loadings are used to estimate new communalities that replace the old communality estimates in the diagonal. Iterations continue until the changes in the communalities from one iteration to the next satisfy the convergence criterion for extraction.
[14] A factor extraction method used to form uncorrelated linear combinations of the observed variables. The first component has maximum variance. Successive components explain progressively smaller portions of the variance and are all uncorrelated with each other. Principal components analysis is used to obtain the initial factor solution. It can be used when a correlation matrix is singular.
[15] All the factors with eigenvalue > 1 are selected. The eigenvalue is the amount of variance of the factor that is contributed to the variance of all variables.
[16] The eigenvalue are listed in a plot in descending order and the points are connected with a straight line. There is an elbow in the line where the difference of the eigenvalue of two factors is the biggest. The first point left to this elbow defines the number of necessary factors. There isn't always a definite solution with this procedure.
[17] The Wilks'Lambda L corresponds to the canonical correlation c with $1-L=c^2$. The squared canonical correlation is the explained variance of the discriminant function as percentage of the total variance.

4 Results

4.1 Death in delivery room

The analysis of the deaths in delivery room comprises several issues. The definition and the collection of those infants is an obvious one and can differ between the centres. However it includes the ethical problem of a physician about an end-of-life decision. To provide any help to the decision, the Swiss Academy of Medical Sciences published first guidelines regarding withdrawal of intensive care in babies with severe malformation or asphyxia in 1996 – revised since then – and guidelines regarding the management of infants below 26 completed gestational weeks were published by the Swiss Society of Neonatology in 2002 [3].

18 (3.0%) infants died in the delivery room in 1996, 21 (3.1%) in 2000 and 24 (3.7%) in 2004, overall 3.3% (95% CI 2.5%-4.0%) The increasing number reflects the fact that more cases of deaths in the delivery room were collected in the database.

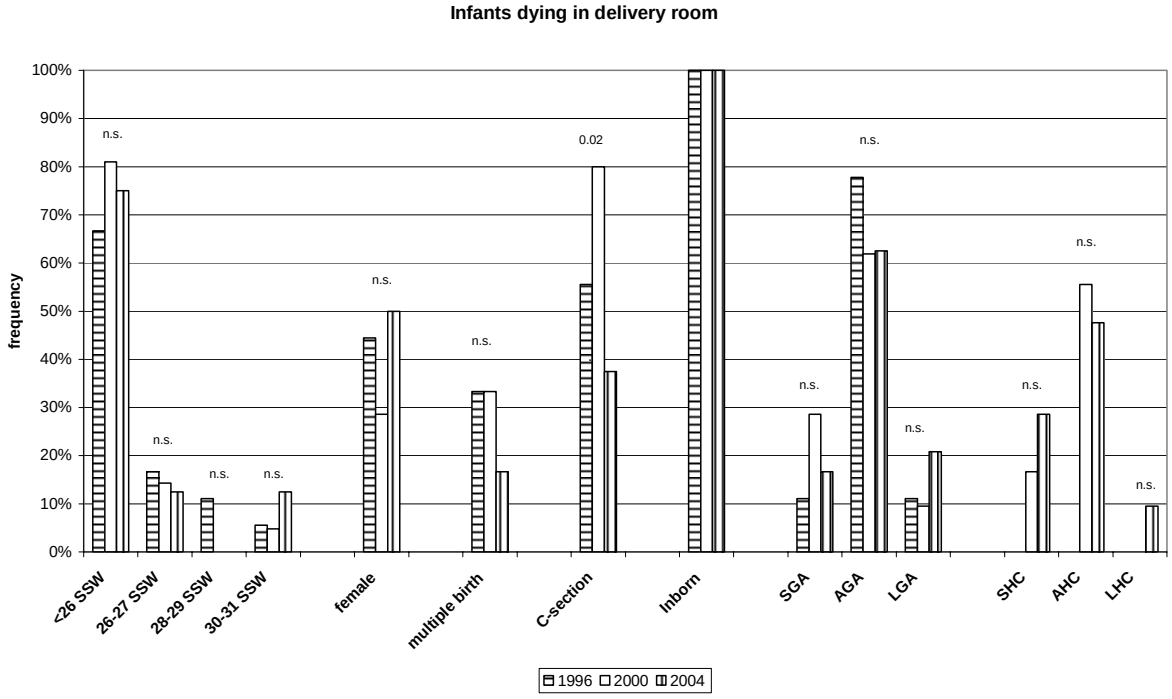
Not astonishingly, most of these infants had less than 26 completed gestational weeks (Figure 1). More deaths with 30 and 31 completed gestational weeks were reported in 2004 than the other years. This could be due to a more comprehensive reporting and not due to a higher mortality rate in the delivery room of this age group. The bigger fluctuation in the frequency of sex, multiple births, mode of delivery, birth weight and head circumference might also be reducible to the reporting and not due to a structural difference of the infants dying in the delivery room. The distribution of the gender, the multiple respectively single births and the LHC didn't differed significantly between all infants and the infants dying in the delivery room overall and in all single years. The distribution of the mode of delivery, SGA, AGA, LGA, SHC and AHC differed significantly overall however only in some years. No outborn infants died in the delivery room and this could be explained by the hypothesis that critical births are mostly performed in perinatal centres and the others weren't collected.

The infants who died in the delivery room had a gestational age between $23^{2}/_{7}$ and $30^{6}/_{7}$ and a birth weight between 380 and 2260g. The ones who were older than $27^{5}/_{7}$ weeks or heavier than 1010g had a major congenital malformation. In total 11 (17.5%) infants – 5 (27.8%) in 1996, 1 (4.8%) in 2000, 5 (20.8%) in 2004 - had a major congenital malformation and their pH of the umbilical artery ranged between 7.26 and 7.35 (median 7.29). The 52 infants with none or minor malformation had a pH-value of the umbilical artery between 6.91 and 7.40 (median 7.23). One of the infants (in 1996) was suspected to have a sepsis. A respiratory distress was diagnosed for 18 (28.5%) infants: two (11.1%) had a Hyaline membrane disease in 1996, three (14.3%) in 2000 and one (4.3%) in 2004 respectively six (33.3%) had another or unknown cause of respiratory distress in 1996, 1 (4.8%) in 2000 and 5 (20.8%) in 2004.

In 2004, 6 infants (25%) received antenatal steroids and 4 (16.7%) got surfactant. three children (12.5%) were mechanical ventilated and one child (4.2%) had CPAP treatment.

In order to get a more precise picture of the true survivor and mortality rate, the infants died in the delivery room were not included in the following chapters. The 23 survivors that are born outside of a perinatal centre are excluded as well: 15 (2.5%) children in 1996 and 8 (1.2%) in 2000.

Figure 1: Distribution of infants who died in the delivery room per different categories and per year.[18]

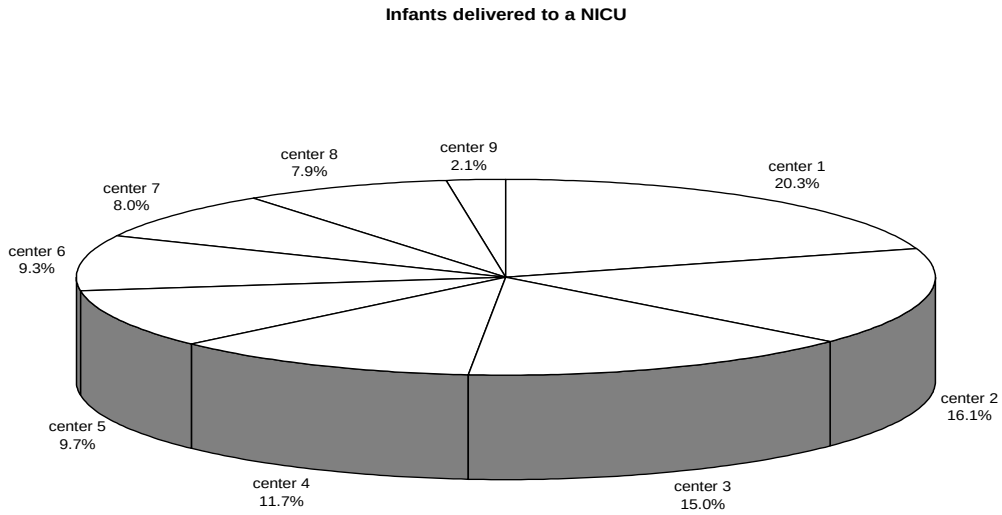


4.2 Demographics of the liveborns in the perinatal centres

The data set included 573 in 1996, 645 in 2000 and 630 infants in 2004 with less than 32 completed gestational weeks. The youngest child was $23^{2}/_{7}$ weeks.

4.2.1 Centre

Figure 2: Total frequency of infants in each perinatal centre.

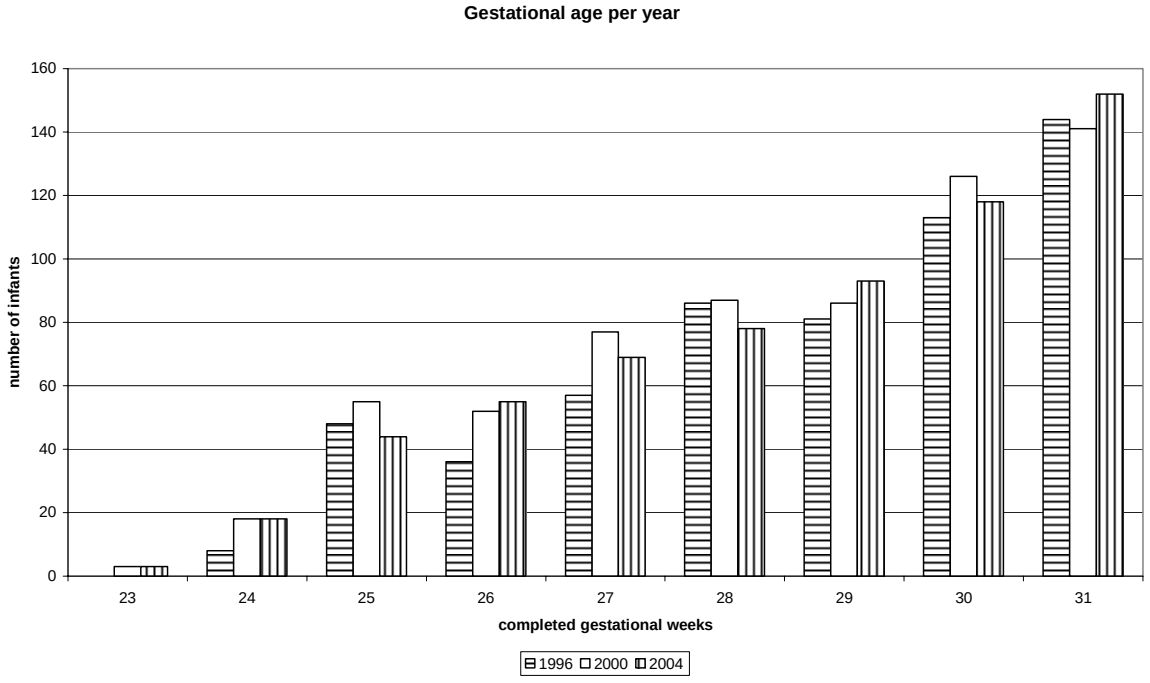


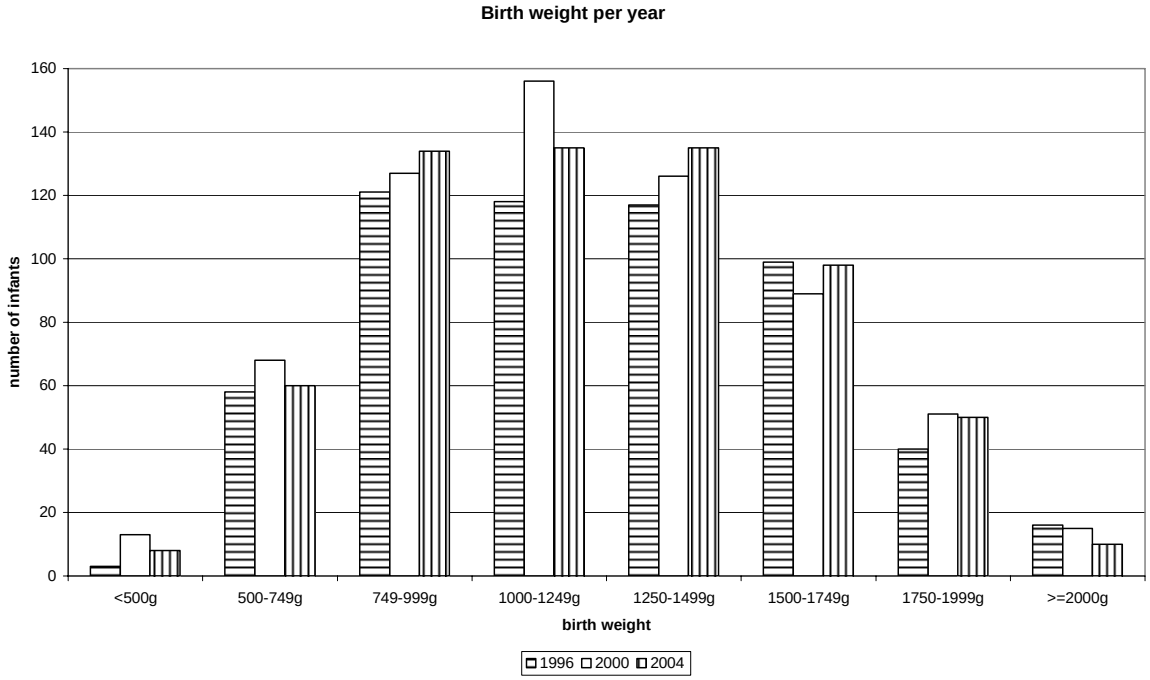
[18] The Chi-square values are shown in the figures and represent the significant difference over the years

The rank regarding number of liveborns changed for some of the perinatal centres over the years[19]. Almost 70% of the infants were born in one of the five university hospitals Basel, Berne, Geneva, Lausanne and Zurich (Figure 2). This rate decreased from 1996 to 2000 and remained stable between 2000 and 2004.

4.2.2 Gestational age and birth weight

Figure 3: Number of infants in each gestational age and birth weight group per year





[19] The name of the NICUs will not be listed due to confidential reasons. The rank of a NICU varies between the figures of the following chapters.

An increase of the frequency can be observed for the infants with less than 26 completed weeks (Figure 3 left): from 9.8% in 1996 to 11.8% in 2000 respectively 10.3% in 2004. The number of infants with 26 and 27 completed gestational age increased as well from 16.2% in 1996 to 20.0% in 2000 respectively 19.7% in 2004

The frequency of the birth weight groups reached a stable level between 700g and 1500g (Figure 3 right). The minimal weight amounted to 370g. 3 (0.5%) infants had a birth weight less than 500g in 1996, 13 (2.0%) in 2000 and 8 (1.3%) in 2004.
The distributions of the gestational age and the birth weight didn't differ much between the years (Table 3).

Table 3: Statistics of the gestational age and the birth weight

Gestational age (week)	1996	2000	2004	Total
Mean	29.2	28.9	29.1	29.1
10^{th} percentile	26.0	25.6	25.9	25.9
25^{th} percentile	27.7	27.3	27.4	27.4
Median	29.7	29.4	29.6	29.6
75^{th} percentile	31.0	30.9	30.9	30.9
90^{th} percentile	31.6	31.4	31.6	31.6

Birth weight (g)	1996	2000	2004	Total
Mean	1235	1206	1217	1219
10^{th} percentile	730	716	721	729
25^{th} percentile	930	910	920	920
Median	1220	1190	1200	1200
75^{th} percentile	1520	1480	1500	1500
90^{th} percentile	1744	1754	1735	1740

4.2.3 Head circumference

The range of the head circumference didn't differ between 2000 and 2004: the minimal size was 197mm in 2000 respectively 200mm in 2004 and the maximal one was 450mm in both years. The distribution was quite symmetrical with a mean of 268mm (in both years). The 10^{th} percentile amounted to 230mm and the 90^{th} percentile was 300mm.

Table 4: The mean head circumference (mm) per gestational age groups respective per gender and per year

Head circumference (mm)	2000	2004	Total
<26 completed weeks	234.1	227.6	231.0
26-27 completed weeks	248.1	245.5	246.8
28-29 completed weeks	266.1	268.3	267.2
30-31 completed weeks	288.7	286.8	287.8

Head circumference(mm)	2000	2004	Total
Female	261.5	259.7	260.6
Male	269.4	270.7	270.1

Obviously, the mean head circumference increased with increasing completed gestational age from 231mm of the infants <26 completed gestational weeks to 288mm of the ones with 30-31 completed weeks (Table 4). The female tended to have a smaller mean head circumference than the male, although not significantly (p_C=0.31).

4.2.4 The pH-value of the umbilical artery

The distribution of the pH-value of the umbilical artery had a skewness to the smaller values. The median (mean) value was 7.28 (7.27). The 10^{th} percentile respectively the 90^{th} percentile was 7.15 (7.12 in 2000, 7.18 in 2004) respectively 7.36 (7.35 in 2000, 7.38 in 2004). The lowest pH-values ranged between 6.57 and 7.50[20].
The mean pH-value didn't vary significantly between the gestational age group and the gender (Table 5).

[20] The pH-values above 7.50 were defined as missing values.

Table 5: The mean pH-value of the umbilical artery per gestational age groups respective per gender and per year

pH-value	2000	2004	Total
<26 completed weeks	7.26	7.29	7.27
26-27 completed weeks	7.24	7.27	7.25
28-29 completed weeks	7.24	7.29	7.26
30-31 completed weeks	7.26	7.28	7.27

pH-value	2000	2004	Total
Female	7.25	7.28	7.27
Male	7.24	7.28	7.26

4.2.5 Gender

The distribution of the sex remained stable over the years (p_C=0.64): 267 (46.6%) females in 1996, 316 (49.0%) in 2000 and 295 (46.8%) in 2004. The average frequency of females was 47.5%. The frequency of females varied little between the perinatal centres[21]: between 34.8% and 52.5% in 1996, between 42.4% and 59.8% in 2000 and between 35.4% and 54.0% in 2004. The overall rate of females in all perinatal centres ranged between 43.8% and 53.2%.

The frequency of females with <26 completed weeks stayed at almost the same level of 44% (p_C=0.74). A decreasing non-significant trend from 50.0% in 1996 to 48.1% in 2000 and 44.1% in 2004 (p_C=0.67) can be observed for females with 26 and 27 weeks. The rate of females with 28 and 29 weeks stayed stable at about 49% over the years (p_C=0.95). The one of the oldest age group varied not significantly between 44.5% in 1996 and 49.1% in 2000 and 47.6% in 2004 (p_C=0.66).

The distribution of the gestational age didn't differ significantly (p_C=0.61) between the gender (Table 6). The males were heavier than the females (p_C=0.71, p_L<0.0001).

Table 6: The statistics of the gestational age and birth weight per gender

Gestational age (weeks)	female	male
Mean	29.1	29.0
10th percentile	25.9	25.7
25th percentile	27.4	27.4
Median	29.6	29.6
75th percentile	30.9	30.9
90th percentile	31.6	31.6

Birth weight (g)	female	male
Mean	1180	1254
10th percentile	709	740
25th percentile	900	940
Median	1150	1240
75th percentile	1440	1550
90th percentile	1680	1780

4.2.6 Singletons and multiple births

The number of multiple births increased significantly and linearly (p_C=0.004, p_L=0.001) over the years from 23.0% in 1996, 28.7% in 2000 and 31.4% in 2004 with an average rate of 27.9%. The frequency of multiple births varied between the perinatal centres: between 9.5% and 36.0% in 1996, between 13.1% and 54.5% in 2000 and between 24.0% and 47.9% in 2004, respective between 21.1% and 40.4% over all years.

No clear temporal trend can be found for female of multiple and single births. The rate stayed stable at a level of 47% for the latter (p_C=0.78) and varied between 43% and 51% for the multiple births (p_C=0.21). The females showed no significant different distribution between single and multiple births (p_C=0.17). However the males differed significantly over the years between the single and multiple births (p_C=0.006, p_L=0.001): 24% of the males belonged to a multiple birth in 1996, 27.1% in 2000 and 33.1% in 2004. The odds ratio for the female to be born as multiple birth amounted to 0.99 (p_C=0.94, 95% CI 0.81-1.22).

[21] One centre was excluded because of too small numbers.

The rate of the multiple births with <26 completed weeks varied between 26.8% in 1996, 21.1% in 2000 and 29.2% in 2004; no significant changes (p_C=0.52). A significant increase from 14.0% in 1996 to 28.7% in 2000 respectively 28.5% in 2004 was seen for multiple births with 26 and 27 completed weeks (p_C=0.031). The frequency of multiple births with 28 and 29 weeks increased significantly from 15.6% in1996 to 21.4% in 2000 and 28.1% in 2004 (p_C=0.020, p_L=0.005). 30.4% of the infants with 30 and 31 weeks were born as multiple birth in 1996, 35.6% in 2000 and 36.7% in 2004; no significant increase (p_C=0.27, p_L=0.13).

Astonishingly, the multiple births were significantly older (p_C and p_L<0.0001) than the single births (Table 7). No consistent significant higher birth weight (p_C=0.61, p_L=0.002) was found for the multiple births (Table 7).

Table 7: Statistics of the gestational age and birth weight per single and multiple births

Gestational age (weeks)	multiple birth	single birth
Mean	29.4	28.9
10th percentile	26.0	25.7
25th percentile	27.9	27.3
Median	30.1	29.3
75th percentile	31.1	30.7
90th percentile	31.7	31.4

Birth weight (g)	multiple birth	single birth
Mean	1262	1202
10th percentile	766	703
25th percentile	960	900
Median	1275	1170
75th percentile	1540	1470
90th percentile	1730	1750

4.2.7 Mode of delivery

The frequency of Caesarean section amounted to 71.2% in 1996, 76.2% in 2000, 76.1% in 2004, and on average 74.6%. Only the change between 1996 and 2000 was significantly (p_C=0.049 from 1996 to 2000, p_C=0.97 from 2000 to 2004, p_C=0.05 from 1996 to 2004). Looking at the variability of the mode of delivery in the perinatal centres, a little temporal increase can be found: the minimal and maximal frequency of C-section was 54.5% respectively 81.0% in 1996, 59.0% respectively 87.0% in 2000 and 65.6% respectively 94.6% in 2004. In all three years, the frequency of C-section varied between 68.1% and 86.5%.

49% infants born by Caesarean section were female (p_C=0.99) and the rate remained almost constant between 1996 and 2004. 41.2% of the vaginal delivered children were female in 1996, 50.3% in 2000 and 40.0% in 2004; no significant change (p_C=0.14). Almost 77% of the females were born by C-section in all years weight (p_C=0.31) and a little lower rate of 72% had the males (p_C=0.06). The female didn't have a significant higher risk to be born by C-section than the males (p_C=0.06; OR=1.23, 95% CI 0.99-1.52).

The frequency of C-section increased significantly for the infants with <26 completed weeks from 41.1% in 1996 to 64.5% in 2000 respectively 61.5% in 2004 (p_C=0.018). No significant different rates of C-section could be observed for the other age groups. On average, 80.8% of the infants with 26 and 27 weeks had a C-section (p_C=0.24), 78.5% of the children with 28 and 29 weeks (p_C=0.62) and 73.8% of the one with 30 and 31 weeks (p_C=0.24).

The distribution of the gestational age differed significantly regarding the mode of delivery (p_C<0.0001 and p_L=0.043), mainly because of the younger infants (Table 8). The vaginal delivered children were significantly heavier (p_C=0.018, p_L<0.0001) than the ones born by C-section (Table 8).

Table 8: Statistics of the gestational age and birth weight per mode of delivery

Gestational age (week)	C-section	vaginal delivery
Mean	29.1	28.9
10th percentile	26.1	25.1
25th percentile	27.6	27.0
Median	29.6	29.6
75th percentile	30.9	31.1
90th percentile	31.6	31.6

Birth weight (g)	C-section	vaginal delivery
Mean	1191	1295
10th percentile	720	740
25th percentile	910	953
Median	1165	1300
75th percentile	1455	1610
90th percentile	1690	1844

4.2.8 Birth location

The rate of inborn infants increased significantly (p_C and p_L <0.0001) from 86.9% in 1996 to 88.3% in 2000 and 94.3% in 2004 with an average frequency of the 89.9%. The rate of inborns varied in the perinatal centres between 81.0% and 98.2% in 1996, between 68.8% and 100% in 2000 and between 89.4% and 100.0% in 2004.

In all years, almost 48% (p_C=0.69) of the inborns and 38% (p_C=0.50) of the outborns were female. The females had a little higher yearly and overall frequency of inborns than the males - both with a significant increase (p_C=0.003 for the females, p_C<0.001 for the males). On average 92% of the females and 88% of the males were inborns, a significant higher rate (p_C=0.007; OR=1.53, 95% CI 1.12-2.09).

Table 9: Statistics of the gestational age and birth weight per birth location

Gestational age (week)	Inborns	Outborns
Mean	29.1	29.1
10th percentile	25.9	25.6
25th percentile	27.4	28.0
Median	29.6	29.7
75th percentile	30.9	30.8
90th percentile	31.6	31.6

Birth weight (g)	Inborns	Outborns
Mean	1211	1285
10th percentile	720	802
25th percentile	910	1000
Median	1190	1260
75th percentile	1490	1570
90th percentile	1735	1780

The youngest two age groups didn't show significant different changes of the frequency of inborns. 85.7% of the infants with <26 completed weeks were inborns in 1996, 85.5% in 2000 and 95.4% in 2004 (p_C=0.12, p_L=0.08). The rate for the ones with 26 and 27 weeks varied between 90.3% in 1996 and 93.0% in 2000 respectively 96.0% in 2004 (p_C=0.25, p_L=0.24). A significant increase from 87.4% inborns in 1996 respectively 85.0% in 2000 to 95.3% in 2004 was seen for the children with 28 and 29 weeks (p_C=0.005, p_L=0.019). Also the rise from 85.6% in 1996 to 89.1% in 2000 respectively 92.6% in 2004 was significantly for the oldest age group (p_C=0.036, p_L=0.010).

The distribution of the gestational age didn't differ significantly (p_C=0.41) for the birth location (Table 9). The inborns were not consistently significantly lighter (p_C=0.98, p_L=0.014) than the outborns.

4.2.9 Small, appropriate and large for gestational age

SGA infants tended to increase (p_C=0.38, p_L=0.17) over the years: 9.4% in 1996, 10.5% in 2000 and 11.9% in 2004. On average, the rate of SGA was 10.7%. The variability of SGA children within 8 perinatal centres decreased over the same period: the minimal and maximal rate was 3.6% respectively 16.0% in 1996, 7.5% respectively 15.2% in 2000 and 8.0% respectively 13.8% in 2004.
AGA and LGA infants decreased from 1996 to 2004. The rate of AGA was 83.4% in 1996, 82.6% in 2000, 81.7% in 2004, and on average 82.6%, always more than 80% and no significant decrease (p_C=0.75, p_L=0.45). The variability of AGAs within the same perinatal centres amounted to 76.5%

minimal and to 90.5% maximal in 1996, 77.1% respectively 87.3% in 2000 and 78.6% respectively 86.0% in 2004.
LGA added to 7.2% in 1996, 6.8% in 2000, 6.3% in 2004, and on average 6.8%, always less than the expected 10% and no significant decrease either (p_C=0.85). The variability of LGA within perinatal centres fluctuated without contemplating the same centres: the minimal rate was 4.0% respectively the maximal rate was 9.1% in 1996, 2.0% respectively 12.5% in 2000 and 2.1% respectively 9.2% in 2004.

Grouped by gestational age, the rate of SGA children amounted to 5.1% for the infants with <26 completed weeks, 17.6% for the ones with 26 and 27 weeks, 11.4% for the ones with 28 and 29 weeks and 9.2% for the oldest age group. The rates increased for the youngest two and for the oldest group over the years. The overall SGA rate of the younger two age groups was significantly different from the overall SGA rate due to the small number of infants (<26 weeks p_C=0.013, 26-27 weeks p_C<0.001, 28-29 weeks p_C=0.66, 30-31 weeks p_C=0.10).
86.8% of the youngest age group were AGA children, 76.3% of the ones with 26 and 27 weeks, 82.2% of the ones with 28 and 29 weeks and 90.8% of the oldest age group. The yearly trends were opposite to the one of the SGA infants. Only the AGA rate of the children with 26 and 27 weeks differed significantly from the overall AGA rate (<26 weeks p_C=0.13, 26-27 weeks p_C=0.006, 28-29 weeks p_C=0.84, 30-31 weeks p_C=0.23).
The frequency of LGA infants amounted to 8.1% of the first, 6.1% of the second, 6.5% of the third and 7.5% of the last age group. The rates of the youngest two age groups increased over the years, the one of the infants with 28 and 29 weeks decreased and the frequency of the oldest children remained stable over the years. No significance was seen between the LGA rates of the single age groups and the overall LGA rate (<26 weeks p_C=0.48, 26-27 weeks p_C=0.64, 28-29 weeks p_C=0.81, 30-31 weeks p_C=0.88).

On average females contributed 45.7% to SGA, 48.2% to AGA and 42.4% to LGA. None of the groups differed significantly (SGA p_C=0.54, AGA p_C=0.27, LGA p_C=0.78) from the rate of females (47.3%). A temporal trend can't be shown for each group either. The females didn't have a significant lower risk to be born as a SGA infant (p_C=0.50; OR=0.90, 95% CI 0.67-1.22) respectively LGA one (p_C=0.21; OR=0.79, 95% CI 0.55-1.14) compared to the AGA children than the males.

4.2.10 Small, appropriate and large head circumference

SHC infants were 8.2% of all infants in 2000 and 8.9% in 2004. The frequency of AHC infants amounted to 82.7% in 2000 and 85.2% in 2004 respectively the one of LHC children was 9.1% in 2000 and 6.0% in 2004. Only the rate change of the latter was significantly (SHC p_C=0.65, AHC p_C=0.24, LHC p_C=0.035).
Two centres that contained a zero percent frequency in one of the years were excluded to determine the variability of the three groups within the perinatal centres. For the group of SHC infants, the variability within the perinatal centres increased over time: the minimal frequency was 4.9% respectively the maximal frequency was 14.3% in 2000 and 4.4% respectively 18.5% in 2004. The minimal frequency of AHC children amounted to 73.7% respectively the maximal frequency was 85.4% in 2000 and 72.8% respectively 89.7% in 2004. For the group of LHC infants, the minimal frequency was 4.3% in 2000 and 2.4% in 2004 respectively the maximal frequency was 16.7% in 2000 and 8.6% in 2004.

The frequencies of SHC, AHC and LHC children in the gestational age groups showed a similar pattern as the ones of the SGA, AGA and LGA infants. On average, 7.6% of the children with <26 completed weeks had a too small head circumference, 14.5% of the ones with 26 and 27 weeks, 8.4% of the ones with 28 and 29 weeks and 6.5% of the ones with 30 and 31 weeks. The AHC rate

amounted to 84.7% in the first age group, 77.8% in the second, 85.0% in the third and 93.5% in the last group. The frequency of LHC infants was 7.6%, 7.7%, 6.6% respectively 8.8% in the corresponding age group. Only the SHC and the AHC rate of the infants with 26 and 27 weeks differed significantly from the overall SHC (p_C=0.003) respectively AHC rate (p_C=0.020).

50.5% of the SHC infants, 47.2% of the AHC and 50.5% of the LHC children were female. None of the three rates didn't differ significantly (SGA p_C=0.54, AGA p_C=0.27, LGA p_C=0.78) from the overall rate of females (47.3%). The females didn't have a significant higher risk to be born as SHC infant (p_C=0.53; OR=1.14, 95% CI 0.76-1.70) respective as LHC one (p_C=0.54; OR=1.14, 95% CI 0.75-1.74) compared to the AHC children than the males.

4.2.11 APGAR score

After 1 minute only 7.1% of the children had an APGAR score smaller than 2 (Table 10). The 50th percentile of the APGAR score after 1 minute amounted to 6 and it rose as expected to 8 after 5 and to 9 after 10 minutes. 65.3% of the children had a score above 7 after 5 minutes and the amount increased to 82.2% after 10 minutes.
21.2% of the infants had a 1-minute APGAR score below 4, 34.0% a score 4-6 and 44.8% a score above 6. After 5 minutes, the score was below 4 for 3.0%. 16.3% of the infants had a score 4-6 and 80.7% had a score above 6. Only 1.3% of the children had a 10-minutes APGAR score below 4, 6.5% were in the middle group and 92.2% had a score above 6.

Table 10: Statistics of the APGAR score

	Apgar 1minute	Apgar 5minutes	Apgar 10minutes
10th percentile	2	6	7
25th percentile	4	7	8
Mean	8	8	9
75th percentile	8	9	9
90th percentile	9	10	10

The APGAR score after minute tended to differ between the age groups as expected: the younger the infant, the lower the score. This difference diminished during the first 10 minutes after birth and the APGAR score was the same independent of the gestational age (Table 11).

Table 11: Mean APGAR score per gestational age group

	Apgar 1minute	Apgar 5minutes	Apgar 10minutes
<26 completed weeks	4	7	8
26-27 completed weeks	5	7	8
28-29 completed weeks	6	8	8
30-31 completed weeks	6	8	9

The APGAR score didn't differ between the genders: the mean APGAR score after 1 minute was 6, the one after 5 minute amounted to 8 for the females and the males, and the one after 10 minutes was 8 for the females and 9 for the males.

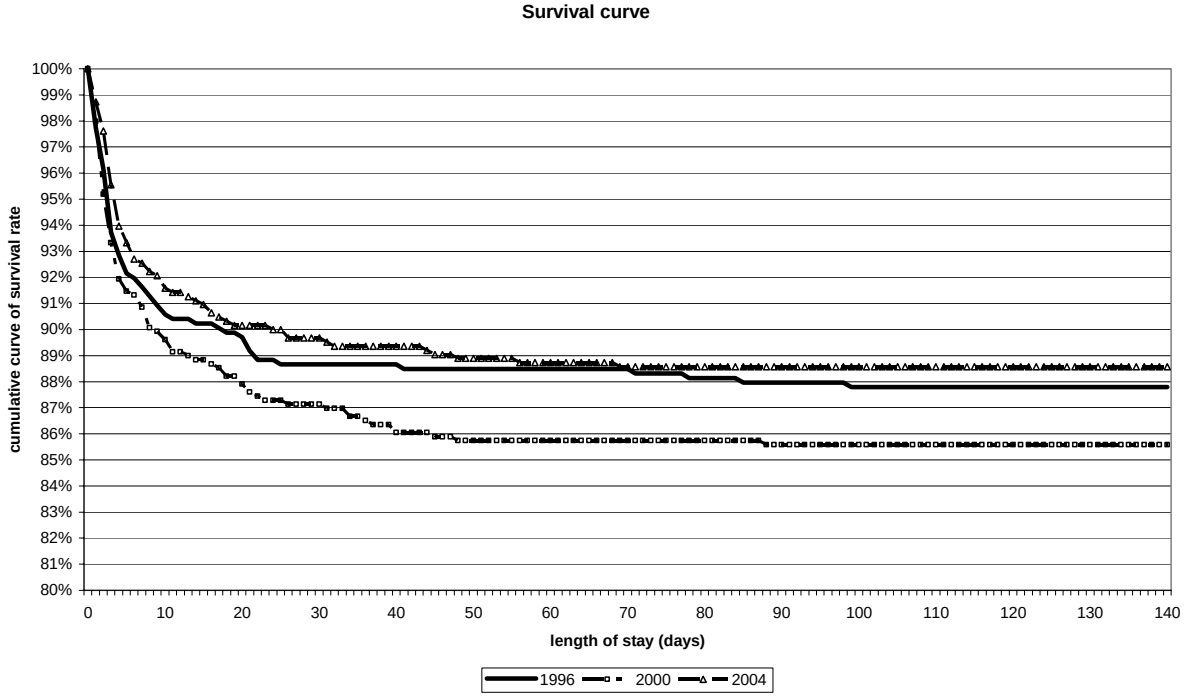
4.3 Mortality of the liveborns in the perinatal centres

4.3.1 Survival analysis

The survival rate[22] amounted to 87.6% in 1996, 85.3% in 2000 and 88.6% in 2004; on average 87.1%. The changes over the years weren't significantly (p_C=0.19). The 95% confidence interval for the corresponding overall mortality rate was 11.4%-14.4% respectively the 95% confidence intervals for the yearly mortality rates were 9.7%-15.1% in 1996, 12.0%-17.5% in 2000 and 8.9%-13.9% in 2004.
The variability of the survival rate in the perinatal centres differed within the years: the minimal respectively the maximal survival rate was 82.9% respectively 92.0% in 1996, 78.8% respectively 95.8% in 2000 and 83.3% respectively 94.0% in 2004 and 84.6% respectively 91.6% on average.

The Kaplan-Meier analysis (Figure 4) showed an overall better survival in 2004 than 1996. The lower survival rate in 2000 than 1996 resulted in the first 48 days of their length of stay, afterwards the difference between the survival curves narrowed[23]. The mean duration till death amounted to 13.2 days in 1996, 14.0 days in 2000 and 10.4 days in 2004.

Figure 4: Kaplan-Meier survivor curve per year.



The survivors had a significant higher gestational age (p_C<0.0001) and birth weight (p_C<0.0001). Furthermore all three APGAR scores were higher (p_C<0.0001). The mean age of the survivors amounted to $29^3/_7$ weeks and was almost equal to the 90th percentile of the deaths (Table 12). The mean age of the deaths was $26^6/_7$ weeks and was almost equal to the 10th percentile of the survivors. The mean birth weight of the survivors amounted to 980g and the one of the births to 904g. The survivors had an average head circumference of 271mm and the deaths had one of 246mm. The distributions of the birth weight respectively the head circumference of the survivors and the deaths

[22] Evans [10] indicates a potential for a selection bias in preterm infant cohort studies that is associated with a higher estimates of survivor, most pronounced at the lower gestations. Due to the reporting problems, this can't be ruled out in the following discussion.
[23] The SPSS wasn't used for the calculation of the Kaplan-Meier curve because it delivered lower yearly survival rates without no clear reason (1996 75.4%, 2000 58.2%, 2004 85.9%). The curves didn't differ significantly (Breslow p=0.18, Tarone-Ware p=0.20).

differed similar to the distribution of the gestational age. The average APGAR score increased for the survivors from 6 after 1 minute to 9 after 10 minutes and for the deaths from 4 after 1 minute to 7 after 10 minutes.

Table 12: Statistics of the survivors and deaths.

Survivals	Gestational age (week)	Birth weight (g)	APGAR 1minute	APGAR 5minutes	APGAR 10minutes
Mean	29.4	1265	6	8	9
10th percentile	26.4	790	2	6	7
25th percentile	28.0	980	5	7	8
Median	29.9	1250	6	8	9
75th percentile	31.0	1533	8	9	10
90th percentile	31.6	1765	9	10	10

Deaths	Gestational age (week)	Birth weight (g)	APGAR 1minute	APGAR 5minutes	APGAR 10minutes
Mean	26.8	904	4	6	7
10th percentile	24.7	520	1	3	5
25th percentile	25.3	700	2	5	6
Median	26.6	818	3	6	8
75th percentile	28.0	1010	5	8	9
90th percentile	29.9	1311	7	9	9

4.3.2 Neonatal mortality rate

An early neonatal (perinatal) death is defined as death of a live born child within the first 7 days of life. The early neonatal mortality rate (Table 13) of the infants who were delivered to a perinatal centres amounted to 8.4% in 1996, 9.1% in 2000, 7.5% in 2004, and on average 8.3% (95% CI 7.1-9.6%); no significant changes between the years (p_C=0.55). These rates were significantly lower than all yearly and overall mortality rates (p_C=0.026 in 1996, p_C=0.002 in 2000, p_C=0.016 in 2004, p_C<0.0001 overall), therefore most of the deaths occurred after the 7th day.
There was a large variability of the early neonatal mortality rate between the single perinatal centres. The maximal rate was 15.9% in 1996, 15.7% in 2000, 14.3% in 2004, and on average 10.8%. There was one centre in all three years with a zero early neonatal mortality rate. The minimal overall rate amounted to 3.9%.

A late neonatal death is after 7 but before 28 completed days of life. 3.2% of the infants who were in the hospital on the 7th day died within the next 21 days in 1996, 4.1% in 2000, 3.1% in 2004, and on average 3.5% (95% CI 2.6-4.4%) (Table 13). The rate changes between the years weren't significantly (p_C=0.60). There was a significant difference between the late neonatal mortality rate and the overall mortality rate (p_C<0.0001 in all years and overall).
The maximal late neonatal mortality rate of all perinatal centres amounted to 7.1% in 1996, 9.1% in 2000, 6.6% in 2004, and on average 6.5%. The minimal rate was 1.4% in 1996, 0% in 2000 and 2004, and on average 1.5%.

The neonatal death is the number of early and late neonatal deaths. This rate (Table 13) amounted to 11.3% in 1996, 12.9% in 2000, 10.3% in 2004, and on average 11.5% (95% CI 10.1-13.0%). The changes between the years weren't significantly (p_C=0.36). There was no significant difference between the yearly and average neonatal mortality rate and the overall mortality rate (p_C=0.58 in 1996, p_C=0.33 in 2000, p_C=0.53 in 2004, p_C=0.21 overall). Therefore the mortality rate resulted mainly from the deaths in the first 28 days after birth.

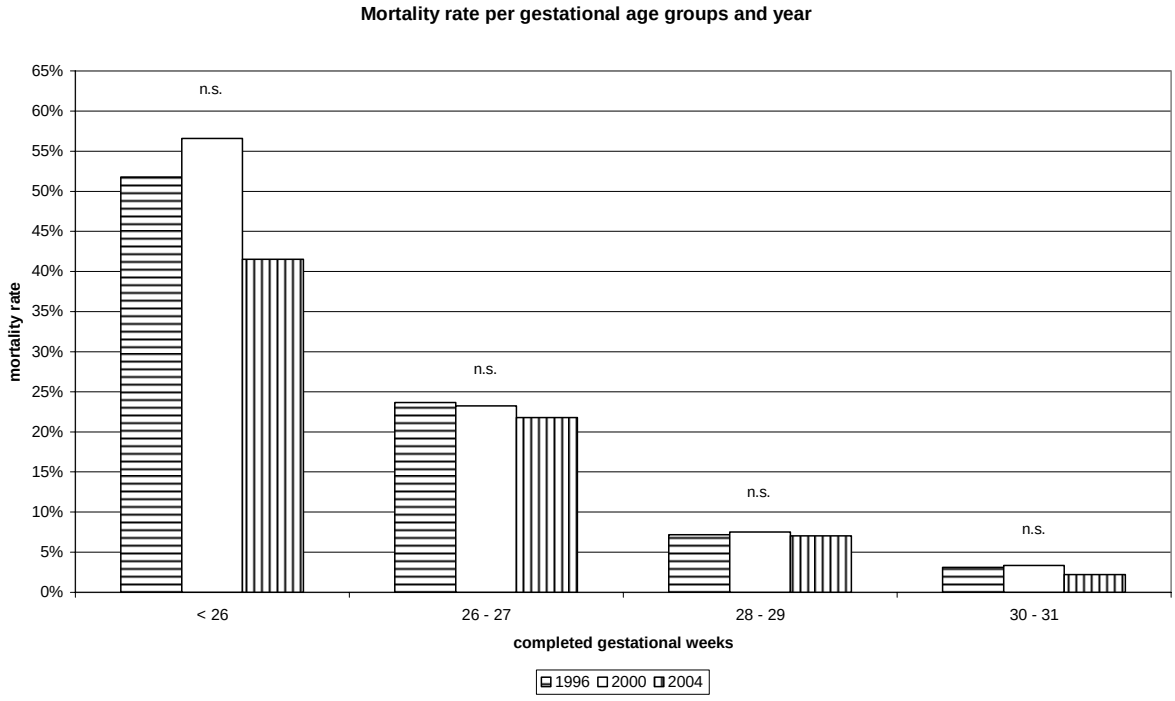
Table 13: Early and late neonatal deaths.

	1996		2000		2004		All infants		
	n	%	n	%	n	%	n	%	95% CI
Life births delivered to centre	573		645		630		1848		
Early neonatal deaths	48	8.4	59	9.1	47	7.5	154	8.3	7.1-9.5
Delivered to home up to 7th day	0	0.0	0	0.0	0	0.0	0	0.0	
Alive infants on 8th day	525		586		583		1694		
Late neonatal deaths	17	3.2	24	4.1	18	3.1	59	3.5	2.6-4.3
Delivered to home on 8th-28th day	6	1.1	12	2.0	11	1.9	29	1.7	
Alive infants on 29th day	502		550		554		1606		
Neonatal deaths	65	11.3	83	12.9	65	10.3	213	11.5	10.1-12.9
All deaths	71	12.4	95	14.7	72	11.4	238	12.9	11.4-14.4

4.3.3 Gestational age

The mortality rate decreased as expected with increasing gestational age (Figure 5). The rate amounted on average 50.3% (95% CI 36.7-50.6%) for the infants with <26 completed gestational age weeks, 22.8% (95% CI 16.2-24.7%) for the infants with 26 and 27 weeks, 7.2% (95% CI 4.5-8.8%) for the infants with 28 and 29 weeks and 2.9% (95% CI 1.6-3.9%) for the children with 30 and 31 weeks.

Figure 5: Mortality rate per gestational age groups and per year.[24]



The infants with <26 completed weeks had a four times higher relative risk to die than the ones who were at least 26 completed weeks (p_C<0.0001; OR=4.05, 95% CI 3.00-5.48). The children with 26-27 weeks died six times more often than the ones who were more than 27 weeks old (p_C<0.0001; OR=6.14, 95% CI 4.28-8.81). The relative risk of 2.6 was calculated for the infants with 28-29 weeks compared to the ones of the oldest age group (p_C<0.001; OR=2.62, 95% CI 1.54-4.46). The odds ratio of the children with 30-31 weeks relative to the ones with <30 weeks amounted to 0.12 (p_C<0.0001; 95% CI 0.07-0.18).

[24] The Chi-square values are shown in the figures and represent the significant difference over the years.

The mortality rate tended to decrease as well from 1996 to 2004: from 51.8% to 41.5% for the infants with <26 completed gestational age weeks (p_C=0.20), from 23.7% to 21.8% for the infants with 26-27 completed weeks (p_C=0.94), from 7.2% to 7.0% for the infants with 28-29 completed weeks (p_C=0.98) and from 3.1% to 2.2% for the infants with 30-31 completed weeks (p_C=0.71). This decrease wasn't continuously for most of the gestational age groups.

Figure 6: Mortality rate per gender and per year

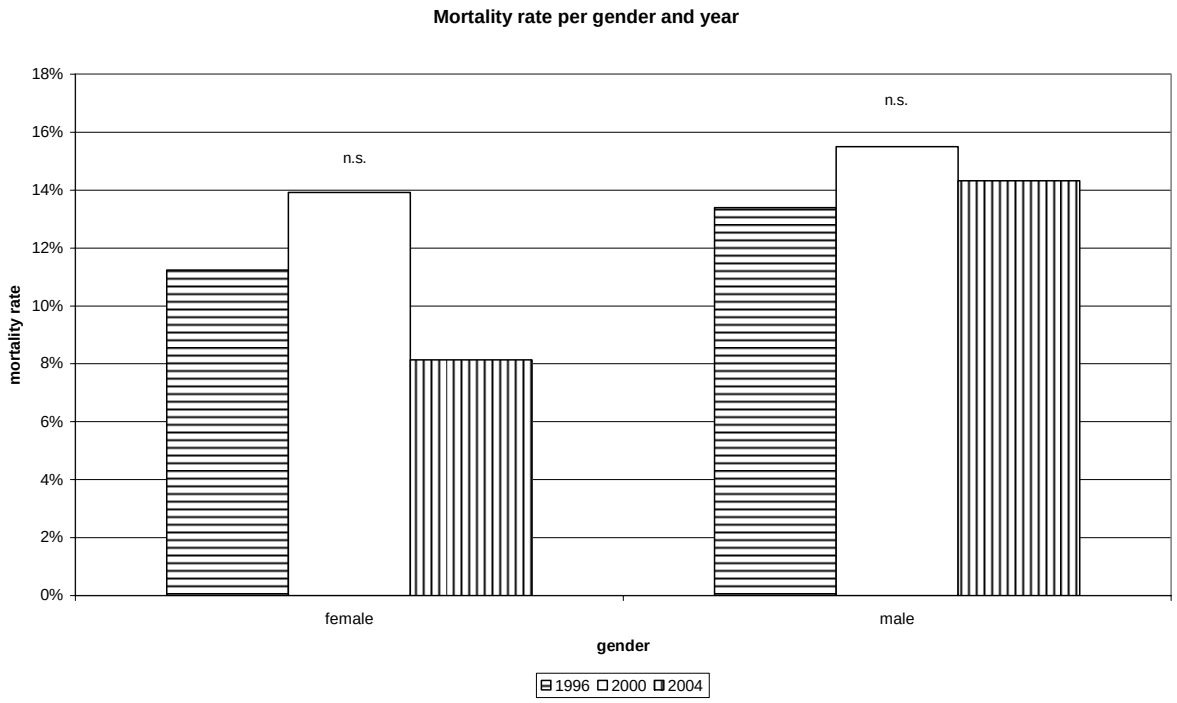
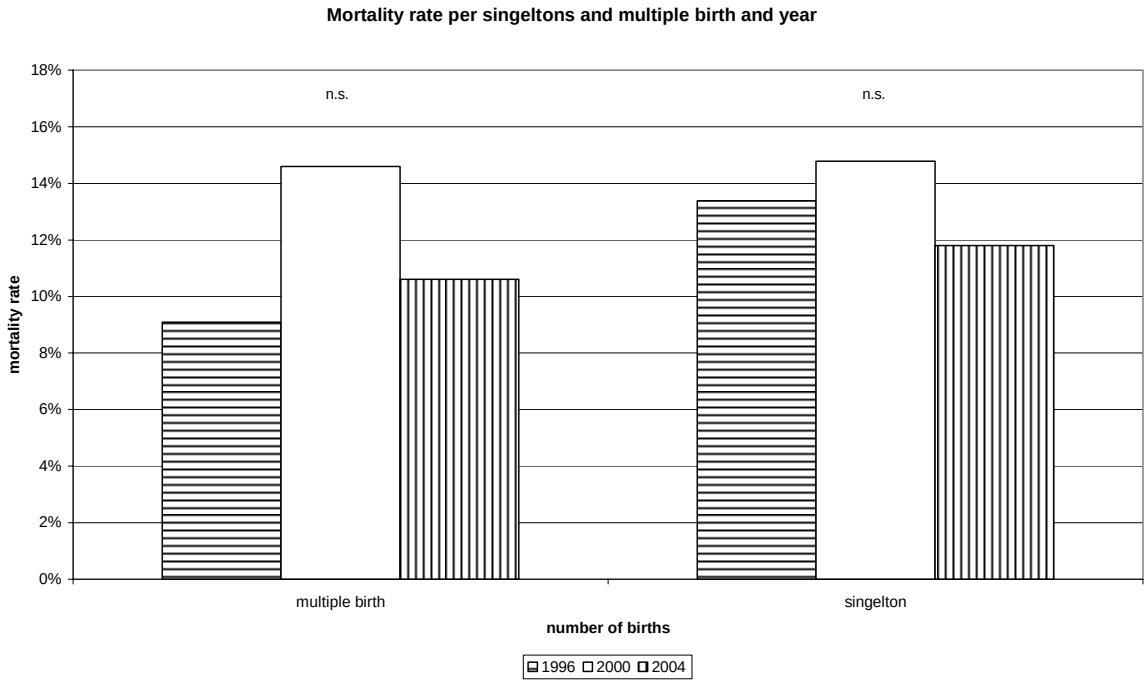


Figure 7: Mortality rate per singletons and multiple births and per year.



4.3.4 Gender

The mortality rate of the female infants (Figure 6) was 11.2% in 1996, 13.9% in 2000, 8.1% in 2004, and on average 11.2% (95% CI 9.1-13.2%). The rate of the male infants amounted to 13.4% in 1996, 15.5% in 2000, 14.3% in 2004, and on average 14.4% (95% CI 12.2-16.6%). Although the mortality rate for male infants was higher than for the female infants in all years, a significant higher mortality rate can only be shown for the year 2004 and for the overall rate (1996 p_C=0.43, 2000 p_C=0.58, 2004 p_C=0.015, overall p_C=0.036). The males had a 1.34 times higher relative risk to die than the females (95% CI 1.02-1.77).

By comparing only 1996 and 2004, the mortality rate of the female infants tended to decrease from 1996 to 2004, however this decrease was not significantly (p_C=0.08). The rate of the male infants tended to increase not significantly (p_C=0.75).

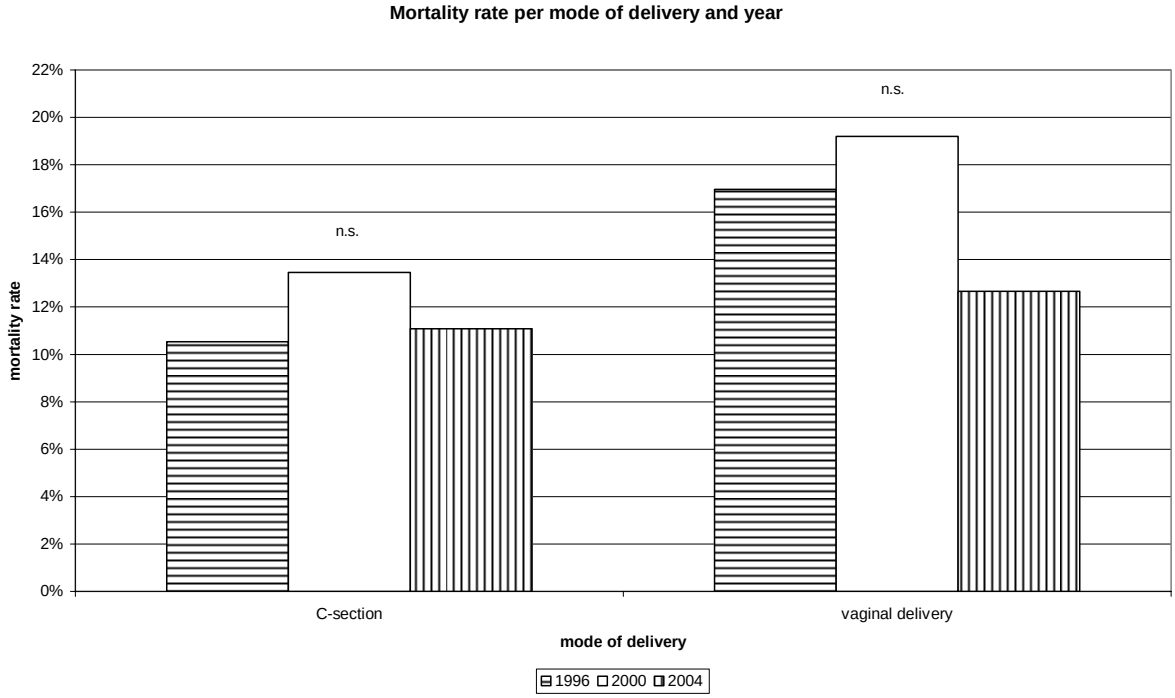
4.3.5 Singletons and multiple births

The mortality rate of single births amounted to 13.4% in 1996, 14.8% in 2000 and 11.8% in 2004 (Figure 7). The rate of multiple births was 9.1% in 1996, 14.6% in 2000 and 10.6% in 2004. On average, the mortality rate for singletons was 13.4% (95% CI 11.5-15.2%) and higher than the rate 11.7% (95% CI 8.9-14.4%) for multiple births. None of the yearly mortality rates differed significantly between both groups (1996 p_C=0.19, 2000 p_C=0.96, 2004 p_C=0.67). The overall mortality rate of the multiple births didn't differ significantly from the one of the singletons (p_C=0.33; OR=0.86, 95% CI 0.63-1.17).

The mortality rates didn't change significantly over the years for the singletons (p_C=0.43) and the multiple births (p_C=0.27).

4.3.6 Mode of delivery

Figure 8: Mortality rate per mode of delivery and per year.



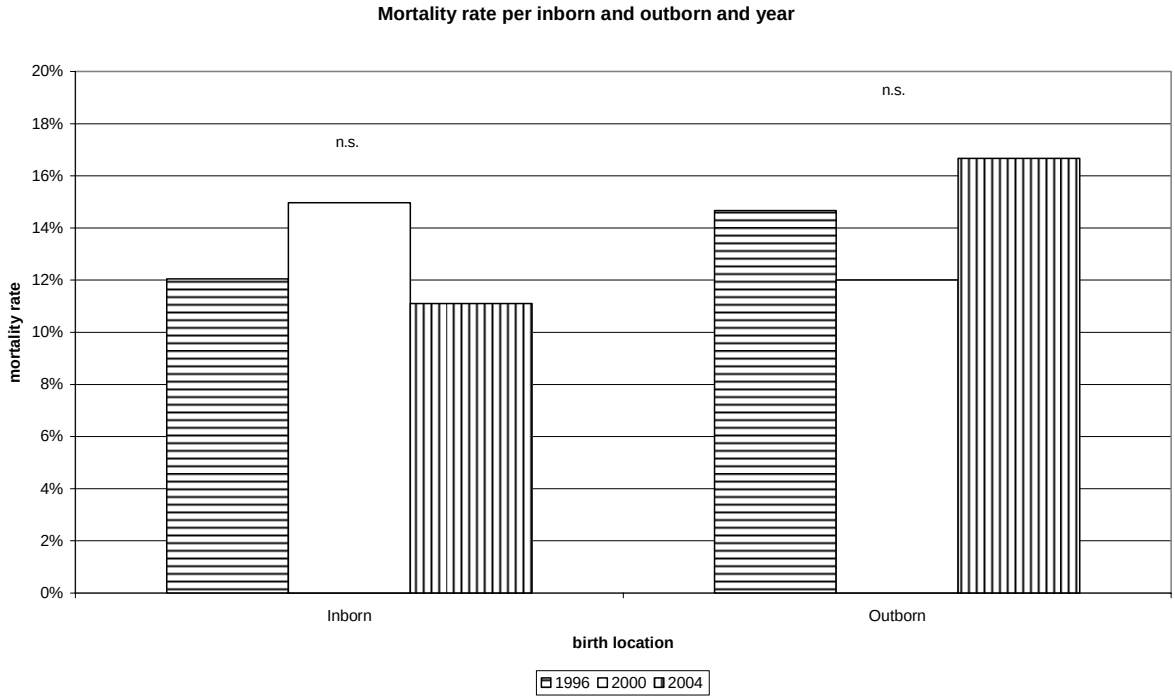
The mortality rate of children born by C-section (Figure 8) was 10.5% in 1996, 13.5% in 2000, 11.1% in 2004, and on average 11.8% (95% CI 10.1-13.5%). The mortality rate of vaginal delivered children amounted to 17.0% in 1996, 19.2% in 2000, 12.7% in 2004, and on average 16.3% (95% CI 12.9-

19.7%). The latter was significantly higher than the first in 1996 and on average (1996 p_C=0.033, 2000 p_C=0.08, 2004 p_C=0.60, overall p_C=0.012). The odds ratio for the children born by C-section amounted to 0.68 (95% CI 0.51-0.92).
There was no significant difference of the mortality rates between the years neither for the vaginal delivered infants (p_C=0.30) nor for the ones born by C-section (p_C=0.34).

4.3.7 Birth location

The mortality rate of the inborn infants (Figure 9) was 12.0% in 1996, 15.0% in 2000, 11.1% in 2004, and on average 12.7% (95% CI 11.1-14.3%). The mortality rate of the outborn infants amounted to 14.7% in 1996, 12.0% in 2000, 16.7% in 2004, and on average 14.0% (95% CI 8.9-19.0%). None of the yearly mortality rates differed significantly between inborn and outborn infants (1996 p_C=0.52, 2000 p_C=0.49, 2004 p_C=0.30) and the overall mortality rate of the inborns wasn't significantly lower than the one of the outborns (p_C=0.63, OR=0.90, 95% CI 0.58-1.39).
The mortality rates of both inborn and outborn children didn't change significantly between the years (inborn p_C=0.12, outborn p_C=0.78).

Figure 9: Mortality rate per birth location and per year.



4.3.8 Small, appropriate and large for gestational age

The mortality rate of the SGA infants (Figure 10) was 14.8% in 1996, 30.9% in 2000, 22.7% in 2004, and on average 23.4% (95% CI 17.4-29.3%). 11.9% of the AGA infants died in 1996, 12.2% in 2000, 9.3% in 2004, and on average 11.1% (95% CI 9.6-12.7%). The mortality rate of the LGA infants amounted to 14.6% in 1996, 20.5% in 2000, 17.5% in 2004, and on average 17.6% (95% CI 10.8-24.3%). Overall, the SGA children died almost 2.5 times more often than the AGA ones (p_C<0.0001; OR=2.43, 95% CI 1.68-3.5). The LGA infants died 1.7 times more often than the AGA ones (p_C=0.029; OR=1.70, 95% CI 1.05-2.77).
The mortality rates didn't change significantly between the years for all three groups (SGA p_C=0.11, AGA p_C=0.27, LGA p_C=0.78). Although the isolated increase for the SGA infants from 1996 to 2000 was significantly (p_C=0.040).

Figure 10: Mortality rate per SGA, AGA and LGA infants and per year.

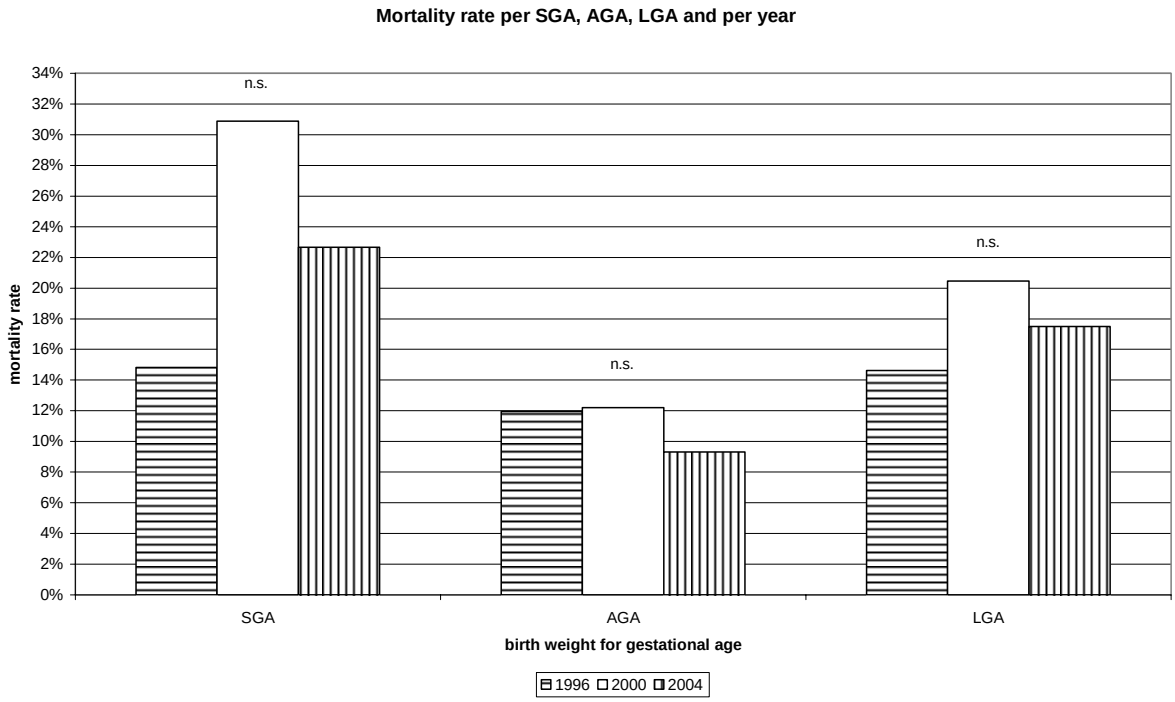
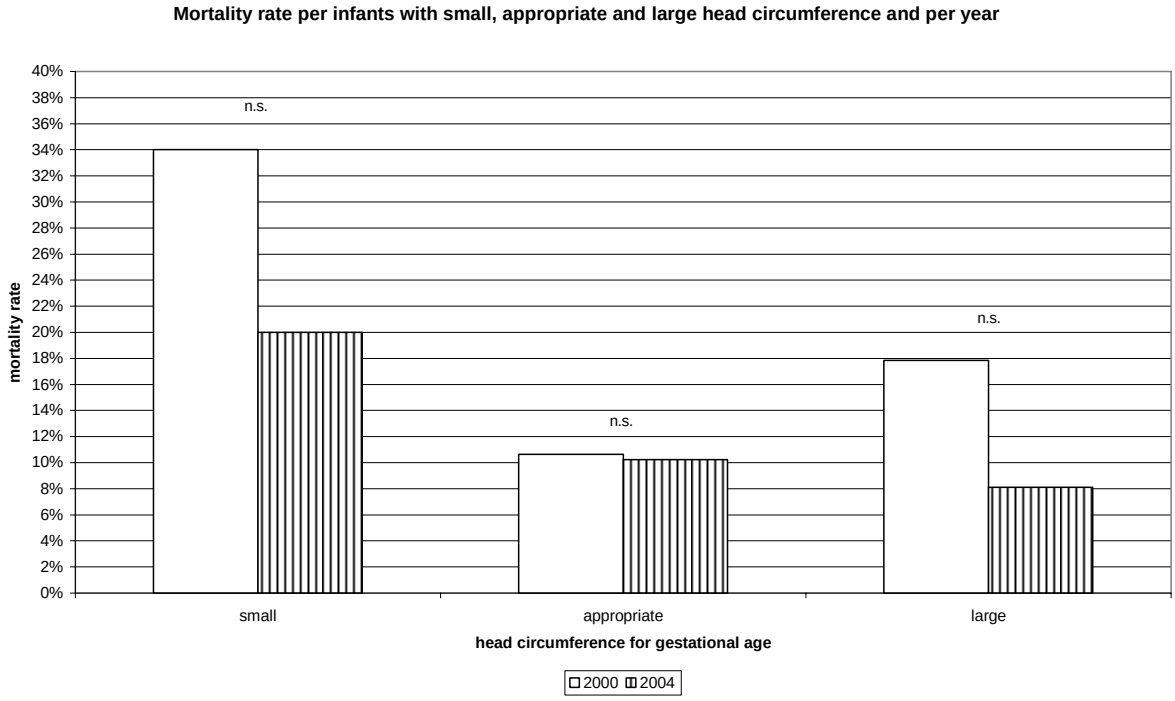


Figure 11: Mortality rate per infants with small, appropriate and large for head circumference and per year.



4.3.9 Small, appropriate and large head circumference

The mortality rate for the SHC infants (Figure 11) was 34.0% in 2000, 20.0% in 2004. 10.7% of the AHC children died in 2000, 10.2% in 2004. The mortality rate for LHC infants amounted to 17.9% in 2000, 8.1% in 2004. The average mortality rate of the SHC infants was 26.7% (95% CI 18.1-35.2%), the one of the AHC children amounted to 10.4% (95% CI 8.6-12.3%) and the one of the LHC infants

was 14.0% (95% CI 6.8-21.1%). The SHC children had overall an almost three times higher relative risk to die than the AHC ones (p_C<0.0001; OR=3.12, 95% CI 1.94-5.03). The mortality rate of the LHC infants didn't differ significantly from the one of the AHC children (p_C=0.29, OR=1.39, 95% CI 0.75-2.59). The odds ratio for the SHC infants relative to the LHC ones amounted to 2.24 (p_C=0.027; 95% CI 1.08-4.64).
The mortality rates of all three head circumference groups didn't change significantly from 2000 to 2004 (SHC p_C=0.11, AHC p_C=0.82, LHC p_C=0.18).

4.3.10 APGAR score

After 1 minute, the mortality rate for the infants with an APGAR score below 4 amounted to 31.3% in 2000 and 32.5% in 2004 (p_C=0.84). 14.4% of the children with a score between 3 and 6 died in 2000, 10.9% in 2004 (p_C=0.27). The mortality rate for a score above 6 was 4.0% in 2000, 3.5% in 2004 (p_C=0.75). The average mortality rate amounted to 31.8% for the lowest score group, 12.6% for the middle and 3.7% for the highest one.
The mortality rate for infants with a 5-minute APGAR score below 4 amounted to 42.9% in 2000 and 64.7% in 2004 (p_C=0.18). For the middle score group, 31.9% of the children died in 2000 and 33.3% in 2004 (p_C=0.82). The lethality for a score above 6 was 8.7% in 2000 and 5.8% in 2004 (p_C=0.07). The average mortality rate amounted to 52.6% for the lowest score group, 32.5% for the middle and 7.3% for the highest one.
After 10 minutes, 61.5% of the infants who had an APGAR score below 4 died in 2000 and all of them - 3 children - died in 2004 (p_C=0.20). The mortality rate for the middle score group amounted to 36.6% in 2000 and 34.1% in 2004 (p_C=0.82). The lethality rate was 11.0% for the infants with a score above 6 in 2000 and 9.2% in 2004 (p_C=0.29). The average mortality rate amounted to 68.8% for the infants of the lower score group, 35.4% for the middle one and 10.1% for the highest one.

4.4 Morbidity of the liveborns in the perinatal centres

4.4.1 Congenital malformation

4.4.1.1 Description

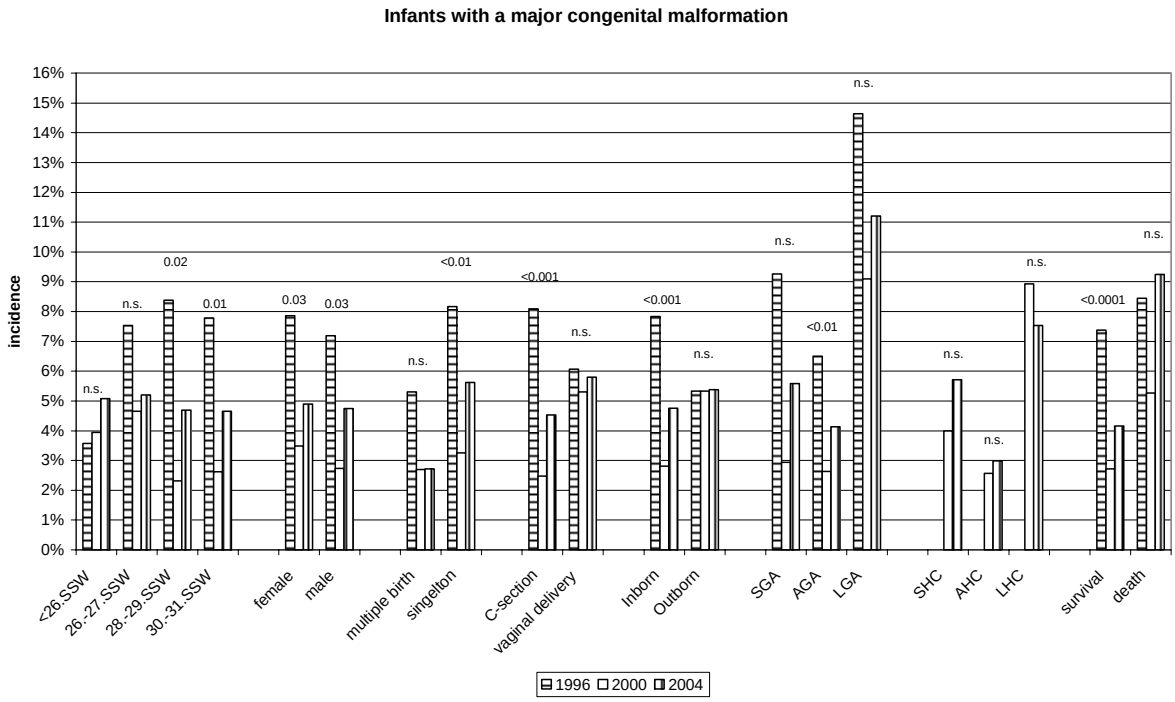
The frequency of infants who were delivered to a perinatal centre and had a major congenital malformation decreased from 7.5% in 1996 to 3.1% in 2000 respectively 4.1% in 2004. The average amount was 4.8% (95% CI 3.8%-5.8%). The incidence of a major congenital malformation changed significantly over the years (p_C<0.001). The maximal amount of infants with a major congenital malformation in a perinatal centre was 9.8% in 1996, 7.1% in 2000, 8.9% in 2004, and on average 7.1%.

The incidence of a major congenital malformation didn't vary much on average between the gestational age groups (Figure 12). The rate amounted on average 5.1% in the group of infants with <26 completed gestational weeks, 5.2% in the group with 26-27 completed weeks, 4.7% in each group with 28-29 respectively 30-31 completed weeks. The average infants of the groups didn't differ significantly (p_C=0.93 between infants with <26 weeks and the ones with 26-27 weeks, p_C=0.85 between infants with <26 weeks and the ones with 28-29 weeks, p_C=0.79 between infants with <26 weeks and the ones with 30-31 weeks, p=0.75 between infants with 26-27 weeks and the ones with 28-29 weeks, p_C=0.70 between infants with 26-27 weeks and the ones with 30-31 weeks, p_C=0.97 between infants with 28-29 weeks and the ones with 30-31 weeks).
No temporal statistical significant difference could be observed for the infants with <26 completed gestational weeks (p_C=0.50) respectively 26-27 weeks either (p_C=0.49). The incidence of infants born with 28-29 weeks with a major malformation decreased significantly over the years (p_C=0.020), the one of the oldest infants as well (p_C=0.013).

On average, 4.9% of the infants with a major congenital malformation were female and 4.7% were male. These rates didn't differ significantly from the ones of the males neither on average (p_C=0.88, OR=1.03, 95% CI 0.68-1.58) nor in any year (1996 p_C=0.75, 2000 p_C=0.59, 2004 p_C=0.63). The incidence of the females with a major malformation decreased significantly from 7.9% in 1996 to 3.5% in 2000 respectively 3.7% in 2004 (p_C=0.026). The rate of the males amounted to 7.2% in 1996, 2.7% in 2000 and 4.5% in 2004, a significant decrease as well (p_C=0.030).

The amout of multiple births with a major congenital malformation differed significantly from the singletons in 2004 and on average, however not in 1996 and 2000 (p_C=0.27 in 1996, p_C=0.72 in 2000, p_C=0.008 in 2004, p_C=0.009 overall). The multiple births had almost 50% lower relative risk to have a major congenital malformation than the singletons (OR 0.47, 95% CI 0.26-0.84). The average rate was 2.8% of the multiple births and 6.0% of the singletons. 5.3% of the multiple births had a major malformation in 1996, 2.7% in 2000 and 1.0% in 2004, no clear significant decrease over the years (p_C=0.06, p_L=0.020) with a significant one between 1996 and 2004 (p_C=0.019). The frequency for the singletons amounted to 8.2% in 1996, 3.3% in 2000 and 5.6% in 2004, no clear significant decrease as well (p_C=0.006, p_L=0.09) with a significant one between 1996 and 2000 (p_C=0.002).

Figure 12: Distribution of infants with major malformation per different categories and per year.



On average, 4.5% of the infants born by C-section had a major congenital malformation and 5.8% of the vaginal delivered infants. The incidence of children born by C-section was 8.1% in 1996, 2.5% in 2000 and 3.6% in 2004, a significant decrease (p_C<0.001). No significant changes between the years were found for vaginal born infants: 6.1% in 1996, 5.3% in 2000 and 6.0% in 2004 (p_C=0.95). However there were no significant changes between the two groups in any year (p_C=0.27 in 1996, p_C=0.40 in 2000, p_C=0.009 in 2004) and on average (p_C=0.19, vaginal delivery versus C-section OR=1.30, 95% CI 0.81-2.06).

The rate of inborns with a major congenital malformation decreased from 7.8% in 1996 to 2.8% in 2000 respectively 4.0% in 2004 (p_C<0.001). The average rate was 4.8%. 5.4% of the outborns had on average a major congenital malformation and this rate varied (p_C=1.00). between 5.3% in 1996 and

2000 and 5.6% in 2004. The frequency of major congenital malformation for inborns and outborns didn't differ significantly in all years (p_C=0.45 in 1996, p_C=0.23 in 2000, p_C=0.67 in 2004) and on average (p_C=0.72, inborn vs outborn OR=0.88, 95% CI 0.45-1.73).

The frequency of SGA infants with a major congenital malformation tended to decrease (p_C=0.32) from 9.3% in 1996 to 2.9% in 2000 respectively 5.3% in 2004. The average rate was 5.6%. The same statistical tendency (p_C=0.69) could be observed for the LGA infants whose rate was 14.6% in 1996, 9.1% in 2000, 10.0% in 2004, and on average 11.2%. The incidence of AGA infants with a major congenital malformation amounted to 6.5% in 1996, 2.6% in 2000, 3.5% in 2004, and on average 4.1%. These changes were significantly (p_C=0.006). The distribution of a major congenital malformation didn't differ significantly between SGA and AGA infants (p_C=0.46 in 1996, p_C=0.87 in 2000, p_C=0.43 in 2004, p_C=0.35 overall) respectively LGA children (p_C=0.40 in 1996, p=0.17 in 2000, p=0.36 in 2004, p=0.07 overall) in every year and on average. A significant difference could be calculated between LGA and AGA infants in every year (p_C=0.049 in 1996, p_C=0.020 in 2000, p_C=0.044 in 2004) and on average (p_C<0.001). SGA cildren didn't have a significant higher relative risk to have a major congenital malformation than the AGA ones (p_C=0.35, OR=1.37, 95% CI 0.71-2.65). However the LGA infants had almost 3 times higher risk than the AGA (p_C<0.001, OR=2.93, 95% CI 1.59-5.39). The odds ratio of the AGA infants relative to the rest of the children amounted to 0.51 (p_C=0.005, 95% CI 0.32-0.83).

An increasing tendency could be found for the SHC infants with a major congenital malformation from 4.0% in 2000 to 7.3% in 2004 (p_C=0.47). The average rate amounted to 5.7%. The rate for AHC and LHC infants remained almost stable between 2000 and 2004. 2.6% of the AHC infants had a major congenital malformation in 2000 and 3.4% in 2004 – no significant increase (p_C=0.43). The frequency of the LHC infants was 8.9% in 2000 and 5.4% in 2004 – no significant decrease (p_C=0.53). The average rate for the AHC infants was 3.0% and 7.5% for the LHC infants.
No statistical significance of major congenital malformations could be observed in all years and on average between SHC and AHC (p_C=0.51 in 2000, p_C=0.16 in 2004; p_C=0.13 overall, OR=1.96, 95% CI 0.80-4.82) and between SHC and LHC infants (p_C=0.31 in 2000, p_C=0.73 in 2004, p_C=0.60 overall). The frequency of major congenital malformation differed significantly between LHC and AHC infants only in 2000 (p_C=0.011 in 2000, p_C=0.52 in 2004) and the LHC children had a 2.64 times higher relative risk to have a major congenital malformation than the AHC ones (p_C=0.019 overall, 95% CI 1.13-6.16). The odds ratio of the AHC infants relative to the rest of the children amounted to 0.44 (p_C=0.014, 95% CI 0.23-0.86).

The rate of survivors with a major congenital malformation decreased significantly from 7.4% in 1996 to 2.2% in 2000 and 2004 (p_C<0.0001). On average, 4.2% of the survivors were diagnosised with a major congenital malformation. The incidence of infants who died during a stay in a perinatal centre and who had a major congenital malformation was 8.5% in 1996, 5.3% in 2000, 15.3% in 2004, and on average 9.2%, no significant difference over the years (p_C=0.53) however with the only significant yearly difference between 2000 and 2004 (p_C=0.030).

4.4.1.2 Mortality rate

The mortality rate of infants with none or a minor congenital malformation amounted to 12.3% in 1996, 14.4% in 2000 and 10.1% in 2004 (Figure 19). There was no significant difference over years (p_C=0.07) except the change from 2000 to 2004 (p_C=0.022). The average rate amounted to 12.3% (95% CI 10.7%-13.8%). An increasing mortality rate can be observed for infants with a major congenital malformation (p_C=0.030) due to the significant increase from 1996 to 2004 (p_C=0.008): from 14.0% in 1996 to 25.0% in 2000 respectively 42.3% in 2004.
The frequency of deaths differed significantly between both groups only in 2004 (p_C<0.001) and overall (p_C<0.001). No significance could be shown for 1996 (p_C=0.74) and 2000 (p_C=0.18). The

infants with a major congenital malformation had a 2.35 times higher relative risk to die than the ones with none or a minor congenital malformation (95% CI 1.42-3.88).

4.4.2 Persistent ductus arteriosus

4.4.2.1 Description

The frequency of infants in the perinatal centres with a persistent ductus arteriosus (PDA) increased significantly (p_C=0.049, p_L=0.015) from 17.1% in 1996 to 19.4% in 2000 and 22.7% in 2000 with an average frequency of 19.8% (95% CI 18.0%-21.6%). The yearly changes were only significantly between 1996 and 2004 (p_C=0.015).
The minimal rate of infants with a PDA resulted by one small perinatal centre: 0.0% in 1996, 6.3% in 2000, 4.2% in 2004, and on average 3.4%. The maximal rates were 32.9% in 1996, 37.3% in 2000, 34.0% in 2004, and on average 30.9%. The distribution of infants with PDA tended to increase from 1996 to 2004 in most of the categories.

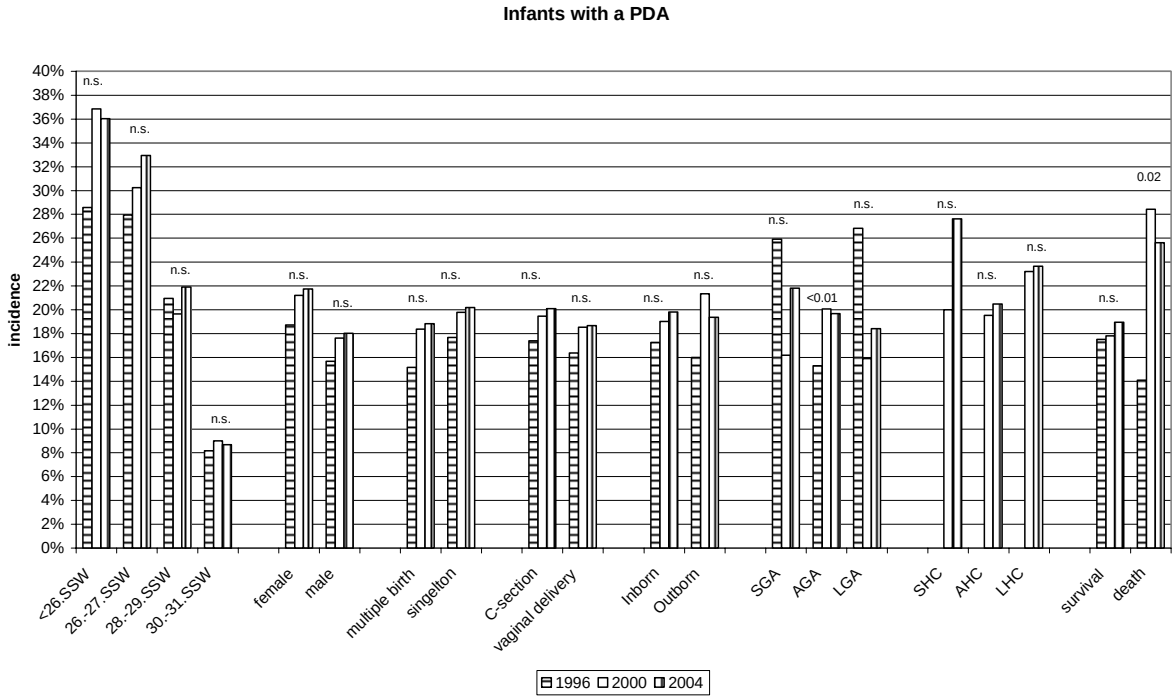
The average rate of PDA seemed to decrease with increasing gestational age (Figure 13): 36.0% of the infants with <26 completed gestational weeks had PDA, 32.9% of the ones with 26-27 completed weeks, 21.9% of the ones with 28-29 completed weeks and 8.7% of the ones with 30-31 completed weeks. The youngest group had significantly more infants with PDA than the groups with >27 completed weeks (p_C=0.46 with the infants with 26-27 completed weeks, p_C<0.001 with the infants with 28-29 completed weeks respectively with the infants with 30-31 completed weeks). The rate of infants with 26-27 completed weeks had significantly more infants with PDA than the infants with >27 completed weeks (p_C<0.001 for all). Also the rate of the infants with 28-29 completed weeks who had a PDA differed significantly from the rate of the ones with 30-31 completed weeks (p_C<0.001).
28.6% of the infants with <26 completed weeks had a PDA in 1996 and the rate tended to decrease to 36.8% in 2000 and 41.5% in 2004 (p_C=0.33, p_L=0.14). The incidence of children with 26-27 weeks amounted to 28.0% in 1996, 30.2% in 2000 and 39.5% in 2004 (p_C=0.14, p_L=0.06). The rate of the infants with 28-29 weeks tended to remain stable between 21.0% in 1996, 19.7% in 2000 and 25.1% in 2004 (p_C=0.44). 8.2% fo the children with 30-31 weeks had a PDA in 1996, 9.0% in 2000 and 8.9% in 2004 (p_C=0.94).

The genders differed significantly only on average: 21.8% of the females and 18.0% of the males had a PDA (p_C=0.046, OR=1.26, 95% CI 1.00-1.59). The single years weren't significantly (p_C=0.34 in 1996, p_C=0.25 in 2000, p_C=0.18 in 2004). Neither the females nor the males had significantly more cases of PDA over the years. 18.7% of the females had a PDA in 1996, 21.2% in 2000 and 25.1% in 2004 (p_C=0.18, p_L=0.07) respectively 15.7% of the males in 1996, 17.6% in 2000 and 20.6% in 2004 (p_C=0.27, p_L=0.11).

The multiple births and singletons didn't a have significant different incidence of PDA in any year (p_C=0.49 in 1996, p_C=0.68 in 2000, p_C=0.70 in 2004) and on average (p_C=0.51, OR=0.92, 95% CI 0.71-1.19). The rate of PDA for multiple births was 15.2% in 1996 and increased to 18.4% in 2000 and 21.7% in 2004 (p_C=0.32, p_L=0.13); the average frequency was 18.8%. 17.7% of the singletons had a PDA in 1996, 19.8% in 2000, 23.1% in 2004 (p_C=0.13, p_L=0.045), and on average 20.2%.

For the mode of delivery, no significant difference could be shown for any year (p_C=0.77 in 1996, p_C=0.79 in 2000, p_C=0.67 in 2004) and overall (p_C=0.51, C-section versus vaginal delivery OR=1.10, 95% CI 0.84-1.43). The vaginal delivered infants had a PDA rate of 16.4% in 1996, 18.5% in 2000, 21.3% in 2004, and on average 18.7%. This increase wasn't significantly (p_C=0.53, p_L=0.26). The frequency of PDA for infants born by C-section increased from 16.4% in 1996 to 18.5% in 2000 and 21.3% in 2004 (p_C=0.11, p_L=0.036) The average rate of C-section born infants with PDA amounted to 20.1%.

Figure 13: Distribution of infants with PDA per different categories and per year.



The same trend and significant result as for the mode of delivery was obtained for the birth location. The rate of inborns with PDA increased from 17.3% in 1996 to 19.0% in 2000 and 22.7% in 2004 (p_C=0.07, p_L=0.023). 19.8% of the inborns were diagnosed on average with PDA. The incidence of PDA in outborns was 16.0% in 1996, 21.3% in 2000, 22.2% in 2004 (p_C=0.63, p_L=0.38), and on average 19.4%. The rate of PDA differed not significantly between inborns and outborns in any year (p_C=0.79 in1996, p_C=0.64 in 2000, p_C=0.93 in 2004) and overall (p_C=0.88, OR=1.03, 95% CI 0.70-1.51).

The only exception of an increasing trend of the incidence of PDA from 1996 to 2004 could be found for SGA and LGA infants. For LGA, the rate tended to decrease from 26.8% in 1996 to 15.9% in 2000 respectively 12.5% in 2004 (p_C=0.22, p_L=0.10). The average rate was 18.4% for the LGA infants. The rate of SGA infants with PDA was 25.9% in 1996, 16.2% in 2000, 24.0% in 2004, and on average 21.8%; no significant change between any two years (p_C=0.37). The AGA infants had an increasing rate of PDA (p_C=0.006, p_L=0.002): from 15.3% in 1996 to 20.1% in 2000 (p_C=0.039) and to 23.3% in 2004 19.7% of the AGA infants had on average a PDA.
The rate of PDA didn't differ significantly between LGA and AGA infants in any year (p_C=0.05 in 1996, p_C=0.50 in 2000, p_C=0.12 in 2004) and overall (p_C=0.72, OR=0.92, 95% CI 0.58-1.47). No significant difference could be shown between SGA and AGA infants (p_C=0.92 in 1996, p_C=0.96 in 2000, p_C=0.14 in 2004; p_C=0.46 overall, OR=1.14, 95% CI 0.79-1.64). The only significant difference of the frequency of PDA could be calculated between SGA and LGA infants in 1996 (p_C=0.043). The rate of PDA didn't differ significantly between SGA and LGA infants in the other years (p_C=0.44 in 2000, p_C=0.88 in 2004) and overall (p_C=0.47). The AGA children didn't have a lower relative risk to have a PDA (p_C=0.74, OR=0.95, 95% CI 0.70-1.28).

For the infants whose head circumference were small (SHC), appropriate (AHC) or large (LHC) for their gestational age the incidence of PDA didn't increase significantly from 2000 to 2004. 20.0% of the SHC infants had a PDA in 2000 and 34.5% in 2004 (p_C=0.10); on average 27.6%. The rate of PDA for AHC infants was 19.5% in 2000, 21.4% in 2004 (p_C=0.46), and on average 20.5%. The frequency

of LHC infants with PDA remained almost stable: 23.2% in 2000, 24.3% in 2004 (p_C=0.92), and on average 23.7%.
In general the SHC had fewer infants with PDA respectively the LHC had more infants with PDA than the AHC infants and therefore the differences weren't significantly in any year and overall with one exception: SHC had a significant higher rate than AHC only in 2004 (p_C=0.94 in 2000, p_C=0.028 in 2004, p_C=0.09 overall, OR=1.48, 95% CI 0.94-2.33). The risk of LHC children's having a PDA wasn't significantly higher than the one of the AHC ones (p_C=0.50 in 2000, p_C=0.68 in 2004, p_C=0.47 overall, OR=1.20, 95% CI 0.73-1.99). The odds ratio of the AHC relative to the rest of the infants didn't differ significantly from one (p_C=0.10, OR=0.74, 95% CI 0.52-1.06).

17.5% of the survivors had a PDA in 1996, 17.8% in 2000, 21.3% in 2004, and on average 18.9%. This increase wasn't significantly (p_C=0.20, p_L=0.11). A significant increase could be found for the frequency of PDA for infants who died in a perinatal centre: from 14.1% in 1996 to 28.4% in 2000 and 33.3% in 2004 (p_C=0.022, p_L=0.009) with an average rate of 19.7%.

4.4.2.2 Mortality rate

The mortality rate of infants without a PDA (Figure 22) who were delivered to a perinatal centre amounted to 12.8% in 1996, 13.1% in 2000, 9.9% in 2004, and on average 11.9% (95% CI 10.3-13.6%). None of these changes were significantly (p_C=0.22).
10.2% of the children with a PDA who were delivered to a perinatal centre died in 1996, 21.6% in 2000, 16.8% in 2004, and on average 1.67%. No significant change could be found (p_C=0.08) althought the yearly differences of the mortality rates between 1996 and 2000 (p_C=0.029) and between 1996 and 2004 (p_C=0.007) were significant.
The mortality rate differed significantly between infants with and without a PDA in 2000 (p_C=0.016), 2004 (p_C=0.021) and overall (p_C=0.015). No significance could be proven for 1996 (p_C=0.48). The children with a PDA had a 1.47 times higher risk dying relative to the ones without a PDA (95% CI 1.07-2.02).

4.4.3 Sepsis

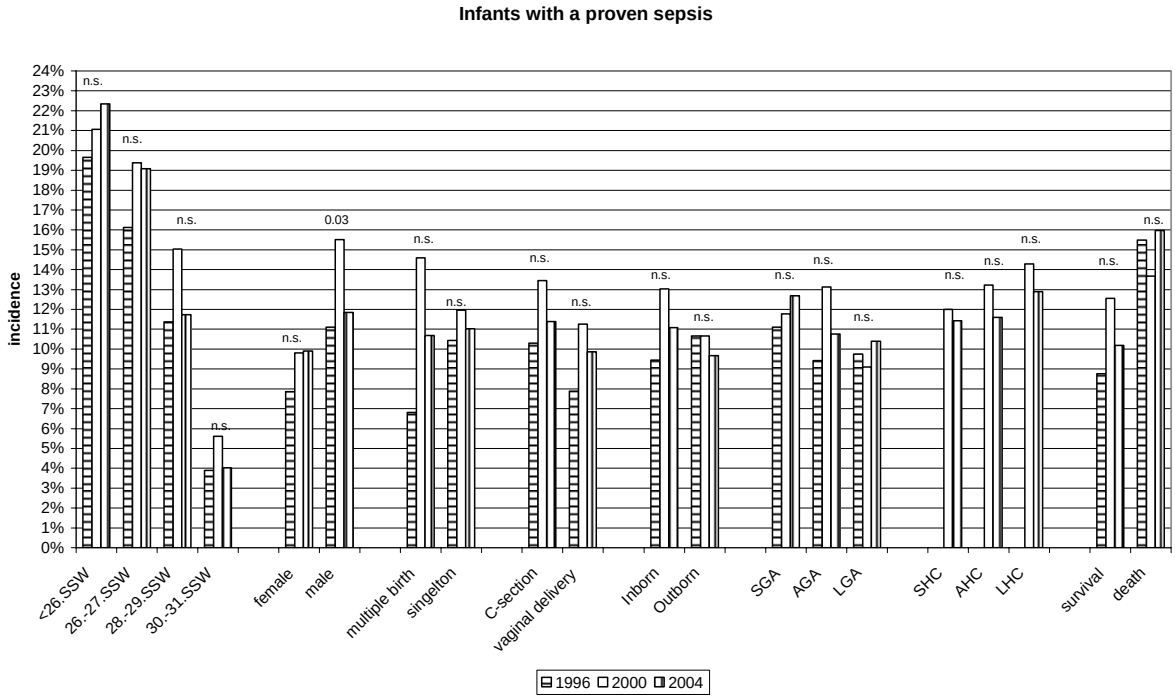
4.4.3.1 Description

The frequency of infants with proven sepsis tended to remain stable (p_C=0.18) during the years: 9.6% in 1996, 12.7% in 2000, 10.3% in 2004, and on average 10.9% (95% CI 9.5-12.4%).
However the rate varied much between the perinatal centres. The minimal rate of proven sepsis was 2.4% in 1996, 1.9% in 2000, 4.2% in 2004, and on average 5.3%. The maximal rate amounted to 21.8% in 1996, 27.3% in 2000, 42.9% in 2004, and on average 28.2%.

The rate of proven sepsis decreased with increasing gestational age (Figure 14). Regarding the average rates, the only two age groups whose incidences didn't differ significantly were the infants with <26 completed gestational weeks and the infants with 26-27 weeks (p_C=0.36). The frequency of sepsis differed significantly between all other pair of age groups (p_C<0.001 between infants with <26 weeks and infants with 28-29 weeks, p_C<0.001 for infants with 30-31 weeks; p_C=0.003 between infants with 26-27 weeks and infants with 28-29 weeks, p_C<0.001 for infants with 30-31 weeks; p_C<0.001 between infants with 28-29 and infants with 30 and 31 weeks).
Infants with <26 completed weeks tended to increase not significantly over the years: from 19.6% in 1996 to 21.1% in 2000 and 26.2% in 2004 (p_C=0.65; p_L=0.38); the average rate was 22.3%. The same is true for infants with 26-27 weeks: the rate tended to increase from 16.1% in 1996 to 19.4% in 2000 and 21.0% in 2004 (p_C=0.66; p_L=0.38) and on average 19.1%. No significant different rates of sepsis could be found for infants with 28-29 weeks: 11.4% in 1996, 15.0% in 2000, 8.8% in 2004 (p_C=0.19),

and on average 11.7%. Sepsis was proven for 3.9% of the infants with 30-31 weeks in 1996, 5.6% in 2000, 2.6% in 2004, and on average 4.0% (p_C=0.20).

Figure 14: Distribution of infants with a proven sepsis per different categories and per year.



The rate of males with proven sepsis varied between 11.1% in 1996, 15.5% in 2000 and 9.0% in 2004 with a significant difference over the years (p_C=0.030). The average frequency was 11.9%. 7.9% of the female had a proven sepsis in 1996, 9.8% in 2000, 11.9% in 2004, and on average 9.9%. The rates didn't differ significantly (p_C=0.65; p_L=0.11). The rate of proven sepsis in the gender differed significantly in 2000 (p_C=0.030), however not in 1996 (p_C=0.19), 2004 (p_C=0.23) and overall (p_C=0.18; female versus male OR=0.82, 95% CI 0.61-1.10).

The rate of sepsis didn't differ significantly between multiple births and singletons in any year and on average (1996 p_C=0.21, 2000 p_C=0.36, 2004 p_C=0.69, overall p_C=0.83; multiple birth versus singleton OR=0.96, 95% CI 0.69-1.34). 6.8% of the multiple births had a sepsis in 1996, 14.6% in 2000, 9.6% in 2004, and on average 10.7%. The rates didn't differ significantly over the years (p_C=0.07) however the yearly change between 1996 and 2000 was significantly (p_C=0.031). The frequency of singletons with a proven sepsis tended to be stable over years (p_C=0.73): 10.4% in 1996, 12.0% in 2000, 10.6% in 2004, and on average 11.0%.

For the mode of delivery, no significant difference of the rate of proven sepsis could be observed neither between C-section born and vaginal delivered infants in any year (p_C=0.38 in 1996, p_C=0.49 in 2000, p_C=0.88 in 2004) and overall (p_C=0.36; C-section versus vaginal delivery OR=.17, 95% CI 0.83-1.66) nor for both groups between any two years. The frequency of C-section born infants with sepsis remained stable (p_C=0.21): 10.3% in 1996, 13.5% in 2000, 10.3% in 2004, and on average 11.4%. 7.9% of the vaginal delivered infants had a proven sepsis in 1996, 11.3% in 2000, 10.7% in 2004, and on average 9.9%; no significant different rates over the years (p_C=0.56).

No significant results could be found for the birth location (1996 p_C=0.74, 2000 p_C=0.56, 2004 p_C=0.34, overall p_C=0.55; inborn versus outborn OR=1.16, 95% CI 0.70-1.94). The incidence of inborns with a proven sepsis tended to be stable (p_C=0.16): 9.4% in 1996, 13.0% in 2000, 10.6% in

2004, and on average 11.1%. The amount of outborns with a proven sepsis tended to decrease (p_C=0.65) from 10.7% in 1996 and in 2000 to 5.6% in 2004. 9.7% of the outborns had on average a proven sepsis.

The SGA infants didn't have significantly more proven sepsis than the AGA ones (p_C=0.41, OR=1.21, 95% CI 0.77-1.89). The LGA children didn't have a significant different incidence of proven sepsis than the AGA ones either (p_C=0.91, OR=0.96, 95% CI 0.53-1.75). The odds ratio for the AGA infants relative to the rest of the infants amounted to 0.90, not significantly different from one (p_C=0.58, 95% CI 0.62-1.31).
The frequency of sepsis tended to remain stable for SGA, AGA and LGA over the years: 11.1% of the SGA infants in 1996, 11.8% in 2000 and 14.7% in 2004 (p_C=0.80; p_L=0.53) respectively 9.4% of the LGA infants had a sepsis in 1996, 9.1% in 2000 and 12.5% in 2004 (p_C=0.87). The average rate was 12.7% for SGA and 10.4% for LGA infants. AGA infants had a proven sepsis with a rate of 9.4% in 1996, 13.1% in 2000, 9.5% in 2004 (p_C=0.09), and on average 10.8%.

The incidence of a proven sepsis for SHC infants tended to decrease from 12.0% in 2000 to 10.9% in 2004 (p_C=0.85), an average rate of 11.4%. The same result was given for AHC children: 13.2% in 2000, 10.0% in 2004 (p_C=0.11), and on average 11.6%. 14.3% of the LHC infants had a proven sepsis in 2000 and this frequency tended to decrease to 10.8% in 2004 (p_C=0.61). The average rate was 12.9%.
The rate of proven sepsis didn't differ between SHC, AHC and LHC infants in any year and overall. The relative risk of SHC children to have a proven sepsis relative to the AHC ones amounted to 0.98 (p_C=0.95, 95% CI 0.52-1.85). The LHC infants didn't have a significant different incidence of a proven sepsis than the AHC ones (p_C=0.71, OR=1.13, 95% CI 0.60-2.13). The odds ratio for the AHC children relative to the rest of the infants was 0.95 (p_C=0.83, 95% CI 0.60-1.52).

For infants delivered to perinatal centres, the frequency of survivors with proven sepsis tended to remain stable (p_C=0.07) between 8.8% in 1996, 12.5% in 2000, 9.1% in 2004, and on average 10.2% with a significant yearly change between 1996 and 2000 was significantly (p=0.048). A higher rate of proven sepsis could be shown for infants who died, however non significant change (p_C=0.60): 15.5% in 1996, 13.7% in 2000, 19.4% in 2004, and on average 16.0%. None of these changes were significant.

4.4.3.2 Mortality rate

Comparing the mortality rate for infants delivered to a perinatal centre with none or suspected sepsis and the one for infants with a proven sepsis, the latter died significantly more in 2004 (p_C=0.007) and on average (p_C=0.008; OR=1.68, 95% CI 1.14-2.46). The rates didn't differ significantly in 1996 (p_C=0.07) and 2000 (p_C=0.76).

The mortality rate for infants with none or suspected sepsis amounted to 11.6% in 1996, 14.6% in 2000, 10.3% in 2004, and on average 12.2%. There were no significant different rates over the years (p_C=0.08) although the change between 2000 and 2004 was significantly (p_C=0.029). The infants with a proven sepsis tended to die over the years with a non-significant different rate (p_C=0.66): 20.0% in 1996, 15.9% in 2000 and 18.8% in 2004. The average mortality rate was 18.8%.

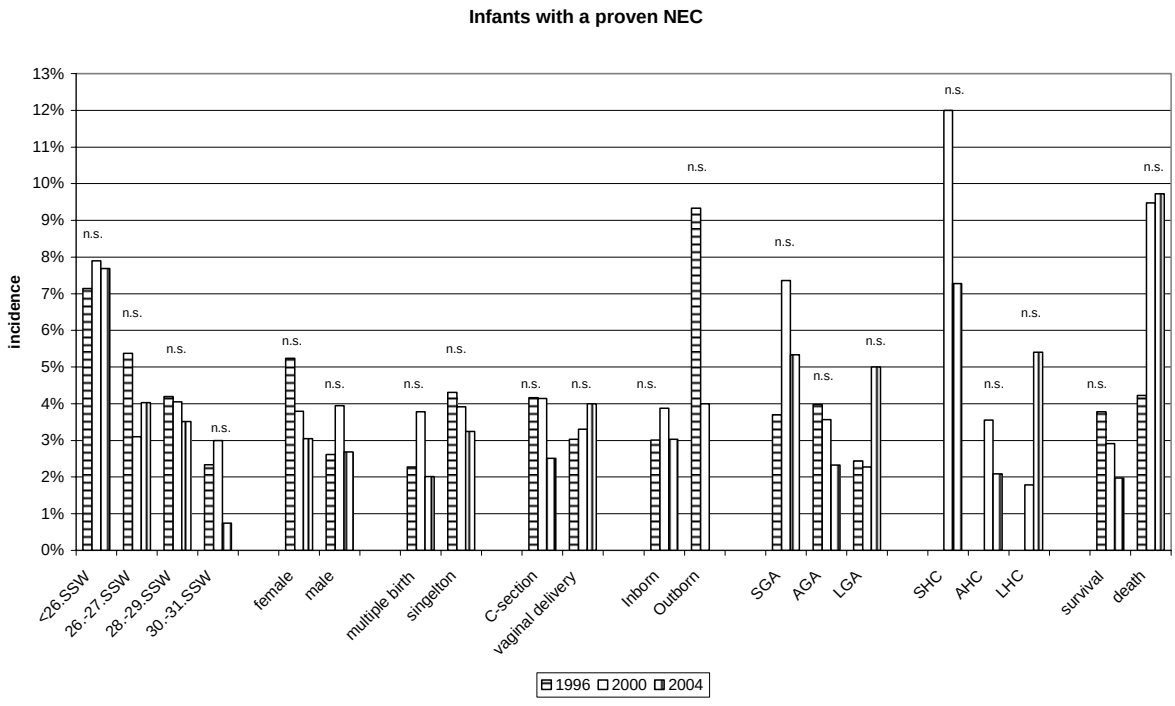
4.4.4 Necrotising enterocolitis

4.4.4.1 Description

The frequency of a proven NEC tended to stay stable over the years: 3.8% in 1996, 3.9% in 2000, 2.9% in 2004, and on average 3.5% (95% CI 2.7-4.4%) of the infants had a proven NEC. The incidences didn't change significantly over the years (p_C=0.54).
The maximal rate of proven NEC within perinatal centres decreased over time: from 11.0% in 1996 to 6.1% in 2000 and 5.3% in 2004. The average maximal rate was 6.8%. Infants with a proven NEC were more likely hospitalised in university hospitals. One of the smaller perinatal centres didn't report any NEC cases at all.

The average rate of a proven NEC decreased with the gestational age (Figure 15): 7.6% of the infants with <26 completed gestational weeks had a NEC, 4.0% of the infants with 26-27 weeks, 3.9% of the infants with 28-29 completed weeks and 2.0% of the infants with 30-31 completed weeks. A significant difference could be proven between the latter and each of the other groups (p_C <0.001 with the infants with <26 weeks, p_C=0.049 with the infants with 26-27 weeks, p=0.041 with the infants with 28-29 weeks) and between infants with <26 weeks and the ones with 28-29 weeks (p_C=0.040). The other groups didn't differ significantly (p_C=0.07 between infants with <26 weeks and the ones with 26-27 weeks, p_C=0.92 between infants with 26-27 weeks and the ones with 28-29 weeks).
The tendency of a stable rate of a proven NEC had the infants with <26 completed weeks: 7.1% in 1996, 7.9% in 2000, 7.7% in 2004, and on average 7.6%. The differences weren't significantly (p_C=0.99). The same result was valid for the other age groups. 5.4% of the infants with 26-27 completed weeks had a proven NEC in 1996, 3.1% in 2000, 4.0% in 2004, and on average 4.0% (p_C=0.70). The rate of infants with a proven NEC and 28-29 completed weeks was 4.2% in 1996, 4.0% in 2000, 3.5% in 2004, and on average 3.9% (p_C=0.94). The frequency of a proven NEC amounted to 2.3% in 1996, 3.0% in 2000, 0.7% in 2004, and on average 2.0% (p_C=0.16).

Figure 15: Distribution of infants with a proven NEC per different categories and per year.



The rate of a proven NEC tended to stay stable over years for male and female infants. The incidence decreased not significantly for females (p_C=0.41) from 5.2% to 3.8% in 2000 and 3.1% in 2004. 4.0%

of the females had averagely a proven NEC. 2.6% of the males had a proven NEC in 1996, 4.0% in 2000, 2.7% in 2004, and on average 3.1% (p_C=0.54). The females and males didn't have a significant different rate of proven NEC in any year (p_C=0.11 in 1996, p_C=0.93 in 2000, p_C=0.77 in 2004) and overall (p_C=0.30, OR=1.30, 95% CI 0.79-2.14).

A similar picture was valid for multiple births and singletons: the rate of proven NEC didn't differ between the two groups in any year and on average (p_C=0.25, multiple birth versus singleton OR=0.70, 95% CI 0.39-1.28). The incidence tended to decrease for singletons from 4.3% in 1996 to 3.9% in 2000 and 3.2% in 2004 (p_C=0.71). 2.3% of the multiple births had a proven NEC in 1996, 3.8% in 2000 and 2.0% in 2004 (p_C=0.53). The average rate was 2.7% for multiple births and 3.8% for singletons.

No significant different occurrence of proven NEC could be shown between vaginal delivered infants and infants delivered by C-section in any year and on average (p_C=0.53 in 1996, p_C=0.63 in 2000, p_C=0.34 in 2004, p_C=0.88 overall, OR=1.04, 95% CI 0.59-1.85). The rate tended to increase for vaginal delivered infants: from 3.0% in 1996 to 3.3% in 2000 and 4.0% in 2004 (p_C=0.89; p_L=0.64). 3.4% of the infants had on average a proven NEC. A decreasing tendency was observed for children delivered by C-section (p_C=0.30; p_L=0.17): from 4.2% in 1996 to 4.1% in 2000 and 2.5% in 2004.The average frequency was 3.6%.

3.0% of inborns had a proven NEC in 1996, 3.9% in 2000, 3.0% in 2004, and on average 3.3%. The rates didn't differ significantly over the years (p_C=0.66). A large however not significant decrease could be observed for outborns (p_C=0.10, p_L=0.033): from 9.3% in 1996 to 4.0% in 2000 and no proven NEC in 2004.On average, 5.4% of the outborns had a proven NEC. A significant different incidence between inborns and outborns could be only shown for 1996 (p_C=0.008). The other rates and the overall rate didn't differ significantly (p_C=0.95 in 2000, p_C=0.30 in 2004, p_C=0.14 on average; inborn versus outborn OR=0.60, 95% CI 0.30-1.20).

The incidence of proven NEC didn't differ significantly between SGA, AGA and LGA infants. Over all years, 5.6% of the SGA infants were proved to have a NEC, 3.3% of the AGA infants and 3.2% of the LGA infants. The risk of SGA infants to have a proven NEC relative to the AGA ones wasn't significantly higher than one (p_C=0.68, OR=1.74, 95% CI 0.89-3.41). The LGA and the AGA infants had almost the same relative risk (LGA versus AGA p_C=0.10, OR=0.98, 95% CI 0.89-3.41). The odds ratio of the AGA children relative to the rest of the infants wasn't significantly lower than one (p_C=0.22, OR=0.69, 95% CI 0.38-1.25).
The incidence of SGA infants tended to remain stable (p_C=0.68) to 3.7% in 1996, 7.4% in 2000 and 5.3% in 2004. None of the changes manifested to be significantly . The rate of proven NEC tended to decrease (p_C=0.31; p_L=0.14) for AGA infants from 4.0% in 1996 to 3.6% in 2000 and 2.3% in 2004. The changes weren't significantly either. For LGA infants, the frequency tended to increase (p_C=0.73) from 2.4% in 1996 respectively from 2.3% in 2000 to 5.0% in 2004, however no significant differences between the years.

A mixed picture was found for the head circumference: a decreasing trend for AHC and SHC infants and an increasing for LHC infants. The rate of proven NEC for SHC infants was 12.0% in 2000 and didn't decrease significantly to 7.3% in 2004 (p_C=0.42). 3.6% of the AHC ones had a proven NEC in 2000 and 2.1% in 2004, no significant decrease (p_C=0.15). No significant increase from 1.8% in 2000 to 5.4% in 2004 was observed for the LHC infants (p_C=0.34). The average rates were 9.5% for SHC, 2.8% for AHC and 3.2% for LHC infants.
Significant differences were seen between the groups. The SHC infants had a 3.65 times higher relative risk than the AHC ones to have a proven NEC (p_C<0.001, 95% CI 1.73-7.72). The incidence was significantly different between SHC and LHC infants only in 2000 (p=0.034 in 2000, p=0.73 in

2004, p=0.07 on average). LHC and AHC infants weren't proven at all to have significant different occurrences of proven NEC (LHC versus AHC p_C=0.79, OR=1.16, 95% CI 0.35-3.87). The odds ratio of the AHC children was significantly lower than one (p_C=0.007, OR=0.41, 95% CI 0.21-0.80).

The rate of the infants who died during the hospital stay and had a proven NEC amounted to 4.2% in 1996, 9.5% in 2000, 9.7% in 2004, and on average 8.0%. The rates didn't differ significantly over the years (p_C=0.38; p_L=0.23). The incidence tended to decrease (p_C=0.21; p_L=0.08) for survivors from 3.8% in 1996 to 2.9% in 2000 and 2.0% in 2004, no significant differences between the years. On average, 2.9% of the survivors were proved to have a NEC.

4.4.4.2 Mortality rate

The mortality rate of the infants with none or suspected NEC amounted to 12.3% in 1996, 13.9% in 2000, 10.6% in 2004, and on average 12.3% (95% CI 10.8-13.8%). 13.6% of the infants with a proven NEC died in 1996, 36.0% in 2000, 38.9% in 2004, and on average 29.2% (95% CI 17.9%-40.6%). The higher and the increasing trend of the mortality rate for the infants with a proven NEC compared to the others were strikingly. The children with a proven NEC died significantly more frequently than the ones without or with a suspected NEC in most of the years (p_C=0.84 in 1996, p_C=0.002 in 2000, p_C <0.001 in 2004) and overall (p_C <0.0001, OR=2.95, 95% CI 1.70-5.13).
The infants with none or suspected NEC died inconsiderably different in the examined years (p_C=0.22). Due to the low incidence of proven NEC, the mortality rates didn't differ significantly between two years for this group either (p_C=0.14).

4.4.5 Retinopathia praematurorum

4.4.5.1 Description

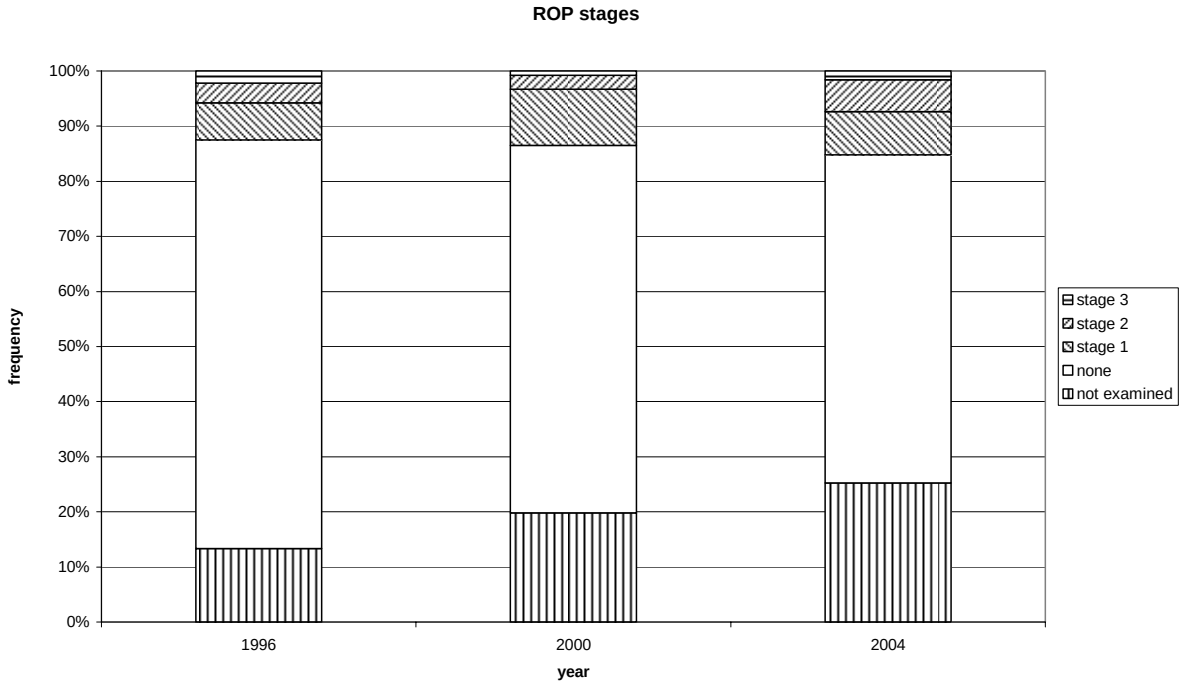
The diagnosis of ROP was made only for a small percentage of the survivors (Figure 16). 13.3% of the infants weren't examined in 1996 and this portion rose to 19.8% in 2000 and 25.3% in 2004, on average 19.7%. No ROP had 74.1% in 1996, 66.7% in 2000 and 59.5% in 2004, on average 66.5%. Adding together these two groups, this portion didn't vary much over the years: 87.5% in 1996, 86.5% in 2000 and 84.8% in 2004. Furthermore the incidence of ROP didn't change significantly over the years (p_C=0.43; p_L=0.20). A ROP was observed on average 13.8% (95% CI 12.1-15.5%)
If a children got the diagnosis of ROP, the frequency decreased with the stages: on average 8.3% of the infants had stage 1, 4.0% stage 2 and 1.5% stage 3. No infant had a ROP stage 4 in the examined years.

The rate of infants with ROP stage 3 amounted to 2.2 % in 1996, 0.7% in 2000, 1.6% in 2004, and on average 1.5% (95% CI 0.9%-2.1%). The incidence didn't differ significantly over the years (p_C=0.14) although the change between 1996 and 2000 was significantly (p_C=0.048 between 1996 and 2000).
The maximal incidence of ROP stage 3 within the perinatal centres was 6.7% in 1996, 2.2% in 2000, 7.2% in 2004, and on average 3.0%. Two of the smaller perinatal centres reported no cases of ROP stages 3 to MNDS.

The rate of ROP stage 3 decreased with gestational age (Figure 17): the average rate for infants <26 completed weeks was 14.3%, 1.9% for infants with 26 or 27 weeks, 0.8% for infants with 28 and 29 weeks and 0.1% for infants with 30 and 31 weeks. The first group had a significant higher rate than the other groups (p_C<0.001 for all groups). The rate of the infants with 26 and 27 weeks differed significantly only from the one of the oldest infant groups (p_C<0.001). The rest of the rates weren't significantly (p_C=0.21 between infants with 26 and 27 weeks and infants with 28 and 29 weeks, p_C=0.05 between infants with 28 and 29 weeks and infants with 30 and 31 weeks).

For the infants with <26 completed gestational weeks, the rate of ROP stage 3 was 22.2% in 1996, 9.1% in 2000 and 13.2% in 2004. The changes between any two years weren't significantly (p_C=0.34). 2.8% of the infants with 26 and 27 completed weeks had ROP stage 3 in 1996, 1.0% in 2000 and 2.1% in 2004. Again, no significant differences between the years could be observed (p_C=0.68). The incidence of infants with 28 and 29 weeks was 1.3% in 1996 and 2004 and none were reported in 2000; no significance trend (p_C=0.36). Only in 1996 there was one case of ROP stage 3 for infants with 30 and 31 weeks, not significantly different from zero (p_C=0.35).

Figure 16: Incidence of ROP for the survivors per year.

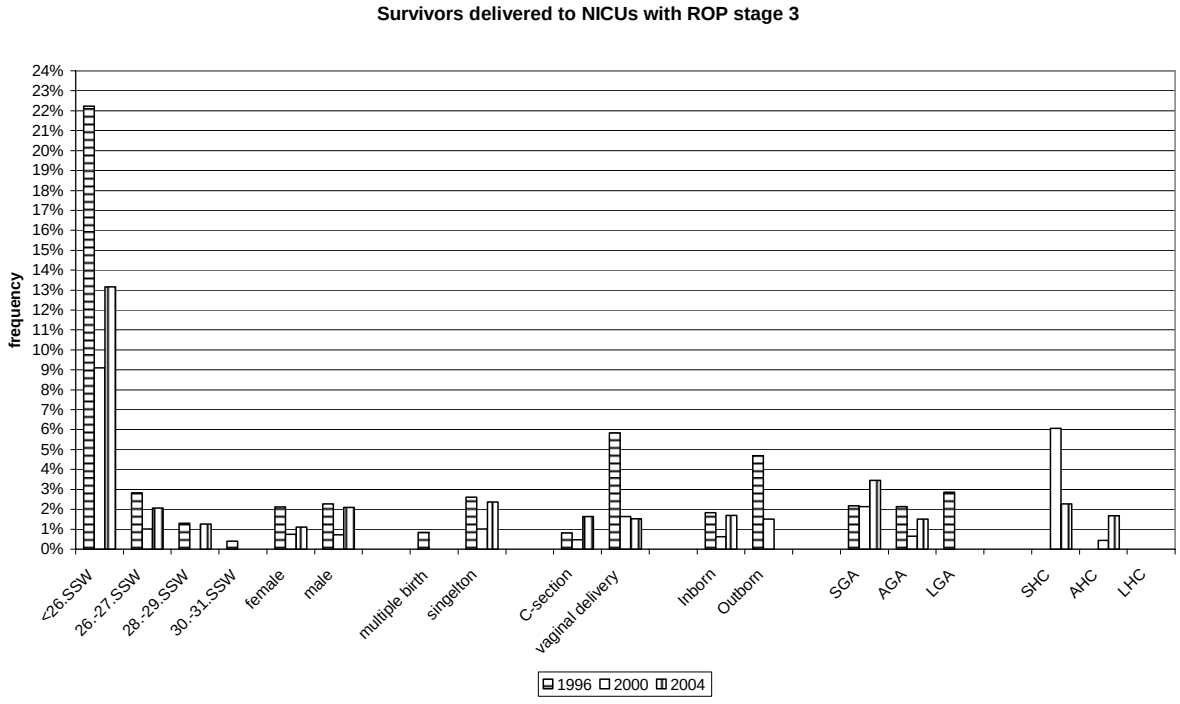


No significant differences between females and males with ROP stage 3 could be observed (p_C=0.51, OR=0.76, 95% CI 0.33-0.71). The incidence of females was 2.1% in 1996, 0.7% in 2000, 1.1% in 2004, and on average 1.3%. 2.3% of the males had ROP stage 3 in 1996, 0.7% in 2000, 2.1% in 2004, and on average 1.7%. The temporal development in both groups was significantly either (females p_C=0.40; males p_C=0.30).

The rate of ROP stage 3 in singletons tended to remain stable within 2.6% in 1996, 1.0% in 2000 and 2.4% in 2004 (p_C=0.23). The average rate was 2.0%. There was only one case (0.8%) of ROP stage 3 for multiple births in 1996, no significant frequency (p_C=0.25). A significant different incidence between singletons and multiple births could be observed only in 2004 (p=0.25 in 1996, p=0.22 in 2000, p=0.037 in 2004) and overall (p=0.008). The multiple births had therefore a significant lower relative risk of ROP stage 3 than the singletons (OR=0.11, 95% CI 0.01-0.81).

Infants delivered by C-section had a significant lower frequency of ROP stage 3 than vaginal delivered infants in 1996 (p<0.001 in 1996, p=0.19 in 2000, p=0.94 in 2004) and overall (p=0.004, OR=0.36, 95% CI 0.14-0.71). However the trends in both groups was diametrically opposed: 0.8% of the infants born by C-section had ROP stage 3 in 1996 respectively 0.5% in 2000 and did not rise significantly to 1.6% in 2004 (p_C=0.21). The incidence of vaginal delivered infants decreased from 5.8% in 1996 to 1.6% in 2000 and 1.5% in 2004 (p_C=0.07, p_L=0.040).The average rate was 0.9% for infants delivered by C-section and 2.6% for vaginal delivered ones.

Figure 17: Distribution of survivors with a ROP stage 3 per different categories and per year.



No significant trends of ROP stage 3 between 1996 and 2004 or differences in any year or overall could be observed for inborns and outborns. The rate tended to remain stable for inborns (p_C=0.21): 1.8% in 1996, 0.6% in 2000 and 1.7% in 2004. The incidence of ROP stage 3 decreased not significantly for outborns from 4.7% in 1996 to 1.5% in 2000 and no case occurred in 2004 (p_C=0.32). The average rate of outborns with ROP stage 3 amounted to 2.2%, however it wasn't significantly higher than the 1.2% for inborns (p_C=0.14 in 1996, p_C=0.45 in 2000, p_C=0.46 in 2004, p_C=0.27 overall; inborn versus outborn OR=0.55, 95% CI 0.18-1.62).

On average, 2.6% of the SGA infants had ROP stage 3, 1.4% of the AGA and 1.0% of the LGA infants. The rates didn't differ at all in any year or overall (SGA versus AGA p_C=0.23, OR=1.91, 95% CI 0.64-.570; LGA versus AGA p_C=0.72, OR=0.69, 95% CI 0.09-5.2; AGA versus rest of the children p_C=0.50, OR=0.71, 95% CI 0.26-1.91).
The incidence of SGA infants didn't vary significantly different between 2.2% in 1996 and 2.1% in 2000 respectively 3.4% in 2004 (p_C=0.89). The rates for AGA infants didn't differ significantly either: 2.1% in 1996, 0.6% in 2000 and 1.5% in 2004 (p_C=0.16). One case (2.9%) of ROP stage 3 were only observed for LGA infants in 1996, but it wasn't significantly different from zero percent (p_C=0.37).

The rate of SHC infants with ROP stage 3 tended to decrease from 6.1% in 2000 to 2.3% in 2004 (p_C=0.40). An increasing trend was observed from 0.4% to 1.7% (p_C=0.07). No cases of ROP stage 3 was reported for LHC infants. On average, 3.9% of the SHC infants had ROP stage 3 and they had a significant higher risk to have a ROP stage 3 than the AHC ones (p_C=0.036, OR=3.72, 95% CI 1.00-13.80). p=0.08 between SHC and LHC, p=0.35 between AHC and LHC). The AHC and LHC children didn't have a significant different overall incidence of ROP stage 3 (p_C=0.35).

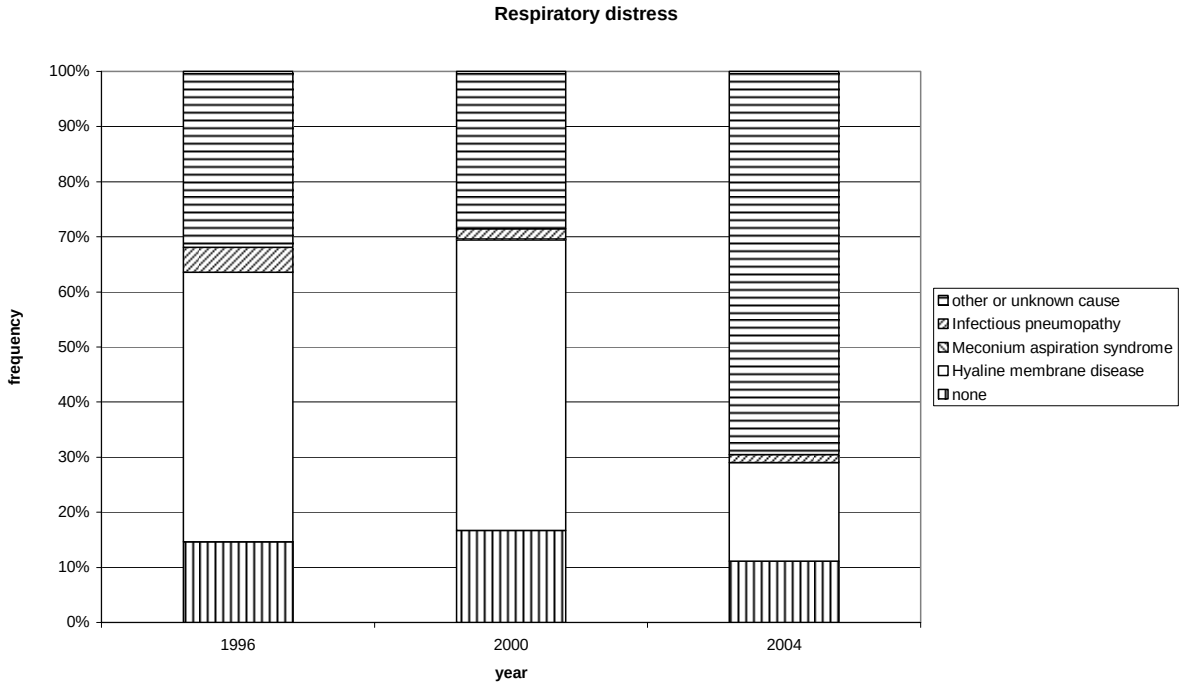
4.4.6 Respiratory distress

4.4.6.1 Description

The diagnosis of a respiratory distress was made for most of the infants who are delivered to a perinatal centre. No respiratory distress (Figure 18) was observed for 14.7% of the infants in 1996,

16.7% in 2000, 11.1% in 2004, and on average 14.2%. In the examined period, only one (0.2% in 2000) infant had a Meconium aspiration syndrome[25]. The main portion of a respiratory distress consisted of the Respiratory distress syndrome/Hyaline membrane disease (RDS): 48.9% in1996, 52.7% in 2000, 17.9% in 2004, and on average 39.7%. The portion of other or unknown causes for respiratory distress amounted to 31.9% in 1996 and 28.5% in 2000 and increased to 69.5% in 2004. The reason is a diffuse definition of RDS and a changed handling of the definition between 2000 and 2004.
RDS and the portion of other or unknown causes are grouped together in the following discussion (called respiratory distress). The exclusion of infectious pneumopathy and Meconium aspiration syndrome means only a small error.

Figure 18: Incidence of respiratory distress per year.



The incidence of the respiratory distress increased significantly (p_C=0.002, p_L=0.002) from 80.8% in 1996 to 81.2% in 2000 and 87.5% in 2004 with an average rate of 83.2% (95% CI 81.5%-84.9%). The variability in the perinatal centres increased over the examined years: the minimal frequency in one of the perinatal centres declined from 68.0% in 1996 to 63.8% in 2000 and 60.4%, an average rate of 69.9%. The maximal rate increased from 85.7% in 1996 to 95.1% in 2000 and 96.9% in 2004, on average 94.6%.

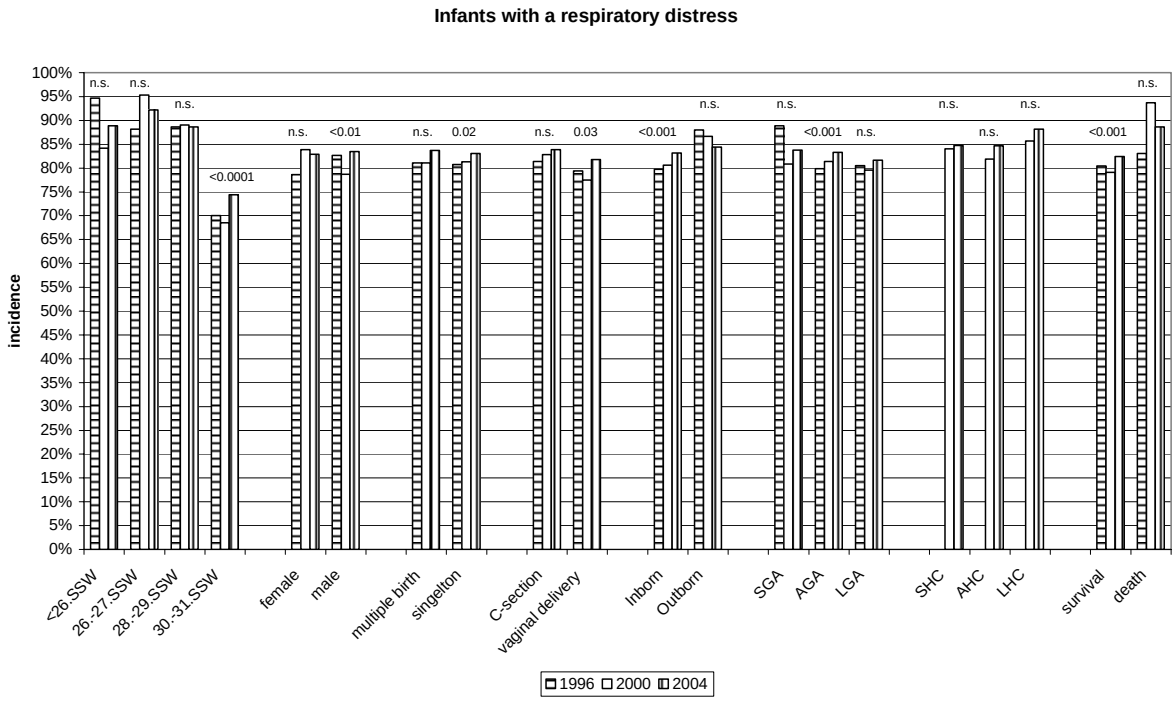
The frequency of infants with <26 completed gestational weeks and respiratory distress tended to remain stable over the years (p_C=0.17): 94.6% in 1996, 84.2% in 2000 and 89.2% in 2004; on average 88.8% (Figure 19). A stable incidence was observed for infants with 26-27 weeks as well: 88.2% in 1996, 95.3% in 2004, 91.9% in 2004 (p_C=0.14) with a significant change between 1996 and 2000 (p_C=0.046), and on average 92.2%. A small range was seen for the infants with 28-29 weeks: 88.6% in 1996, 89.0% in 2000, 88.3% in 2004 (p_C=0.98), and on average 88.6%. The children with 30-31 weeks increased significantly from 70.0% in 1996 respectively 68.5% in 2000 to 84.4% in 2004 (p_C<0.0001) with an average rate of 74.4%.

[25] A mecondium aspiration syndrome is the complication of an intrauterine asphyxia with the sequelae of a severe respiratory distress syndrome immediately after birth. It happens mainly for term, dystrophe and carried-over – defined as born after 42 completed gestational weeks – infants [28].

The average incidence differed significantly between most of the age groups (p_C=0.19 between infants with <26 weeks and the one with 26-27 weeks, p_C=0.94 between infants with <26weeks and the one with 28-29 weeks, p_C<0.001 between infants with <26 weeks and the one with 30-31 weeks, p_C=0.09 between infants with 26-27 weeks and the one with 28-29 weeks, p_C<0.001 between infants with 26-27 weeks and the one with 30-31 weeks respectively between infants with 28-29 weeks and the one with 30-31 weeks).

The females didn't have a clear significant increase of the incidence: 78.7% in 1996 to 83.9% in 2000 and 85.8% in 2004 (p_C=0.07, p_L=0.027), an average rate of 82.9%. The rate for males differed significantly over the years: 82.7% in 1996, 78.7% in 2000, 89.0% in 2004 (p_C=0.21 between 1996 and 2000, p<0.001 between 2000 and 2004, p_C=0.023 between 1996 and 2004), and on average 83.5%. The frequencies didn't differ significantly between females and males in any year and on average (p_C=0.23 in 1996, p_C=0.09 in 2000, p_C=0.23 in 2004, p_C=0.74 overall; female versus male OR=0.96, 95% CI 0.75-1.22).

Figure 19: Distribution of survivors with a respiratory distress per different categories and per year.



The incidence of respiratory distress amounted to the multiple births to 81.1% in 1996 and 2000, 87.9% in 2004, and on average 83.7% (p_C=0.13; p_L=0.08). The rates for singletons increased significantly from 80.7% in 1996 to 81.3% in 2000 and 87.3% in 2004 (p_C=0.017; p_L=0.010) with an average rate of 83.0%. The differences of the incidences between multiple and single births weren't significantly at all (p_C=0.94 in 1996, p_C=0.95 in 2000, p_C=0.84 in 2004, p_C=0.74 overall; multiple birth versus singleton OR=1.05, 95% CI 0.80-1.38).

The frequency of infants born by C-section with a respiratory distress didn't increase significantly (p_C=0.06; p_L=0.020) from 81.4% in 1996 to 82.8% in 2000 and 87.0% in 2004 with an average rate of 83.9%. A significant increase was found for vaginal delivered infants (p_C=0.026): 79.4% in 1996, 77.5% in 2000, 88.7% in 2004, and on average 81.8%. The incidences didn't differ significantly between both groups in any year and on average (p_C=0.59 in 1996, p_C=0.14 in 2000, p_C=0.59 in 2004, p_C=0.29 overall, C-section versus vaginal delivery OR=0.86, 95% CI 0.65-1.14).

The inborn had a significant increase in the incidence of respiratory distress (p_C<0.001; p_L <0.0001): 79.7% in 1996, 80.6% in 2000, 88.4% in 2004, and on average 83.1%. The incidence of the outborn didn't differ significantly (p_C=0.08; p_L=0.06) between 88.0% in 1996, 86.7% in 2000 and 72.2% in 2004 although the decrease between 1996 and 2004 was significantly (p_C=0.041). The average rate amounted to 84.4%. The frequencies differed significantly between inborns and outborns only in 2004 (p_C=0.09 in 1996, p_C=0.21 in 2000, p_C=0.004 in 2004, p_C=0.66 overall; inborn versus outborn OR=0.91, 95% CI 0.60-1.38).

The incidence of respiratory distress of the SGA infants tended to remain stable (p_C=0.47) and was 88.9% in 1996, 80.9% in 2000 and 82.7% in 2004. A significant increase (p_C and p_L<0.001) was observed for AGA children: from 79.9% in 1996 to 81.4% in 2000 and 88.3% in 2004. 80.5% of the LGA infants had a respiratory distress in 1996, 79.5% in 2000 and 85.0% in 2004, no significant differences between the years (p_C=0.79).
The average rate was 83.8% for the SGA, 83.3% for the AGA and 81.6% for the LGA infants. The overall incidences didn't differ significantly between the three groups at all (SGA versus AGA p_C=0.87, OR=1.04, 95% CI 0.69-1.55; LGA versus AGA p_C=0.64, OR=0.89, 95% CI 0.56-1.43; AGA versus rest of the infants p_C=0.87, OR=1.03, 95% CI 0.75-1.41).

The frequency of SHC infants with respiratory distress amounted to 84.0% in 2000, 85.5% in 2004 (p_C=0.84), and on average 84.8%. The change of the incidence of the AHC children between 81.9% in 2000 and 87.3% in 2004 was significantly (p_C=0.015) and the average rate was 84.6%. The incidence of LHC children tended to increase from 85.7% in 2000 to 91.9% in 2004 (p_C=0.37) with an average rate of 88.2%.
The three groups didn't have any significant different frequencies in any year and on average. The SHC and AHC infants had the same relative risk to have a respiratory distress (p_C=0.97, OR=1.01, 95% CI 0.58-1.76). The risk of the LHC children was a bit higher but non significantly either (p_C=0.36, OR=1.35, 95% CI 0.71-2.60). The odds ratio of the AHC infants relative to the rest of the children amounted to 0.87 (p_C=0.53, 95% CI 0.56-1.35).

The incidence of respiratory distress increased for the surviving infants from 80.5% in 1996 respectively from 79.1% in 2000 to 87.5% in 2004 (p_C<0.001). 83.1% of the children who died during their stay in a perinatal centre had respiratory distress in 1996, 93.7% in 2000 and 87.5% in 2004; these rates tended to remain stable over the years (p_C=0.10) although the yearly change between 1996 and 2000 was significantly (p_C=0.030 between 1996 and 2000). The average rate was 82.4% for the survivors and 88.7% for the other group.

4.4.6.2 Mortality rate

The mortality rate for the infants with respiratory distress amounted to 12.7% in 1996, 17.0% in 2000, 11.4% in 2004, and on average 13.7% (95% CI 12.0%-15.4%). The decrease from 2000 to 2004 was significantly (p_C=0.023, p_L=0.46). 15.4% of the children only with RDS died in 1996, 22.1% in 2000 and 14.2% in 2004. The mortality rate for the infants with no respiratory distress tended to remain stable: 8.3% in 1996, 5.6% in 2000, 8.6% in 2004 (p_C=0.17), and on average 7.3% (95% CI 5.6%-11.9%). The differences between the two groups were significantly in 2000 and on average (p_C=0.22 in 1996, p_C=0.003 in 2000, p_C=0.43 in 2004, p_C=0.003 overall). The infants with a respiratory distress had a 1.61 times higher relative risk than the others to die (95% CI 1.09-2.54).

4.4.7 Chronic lung disease

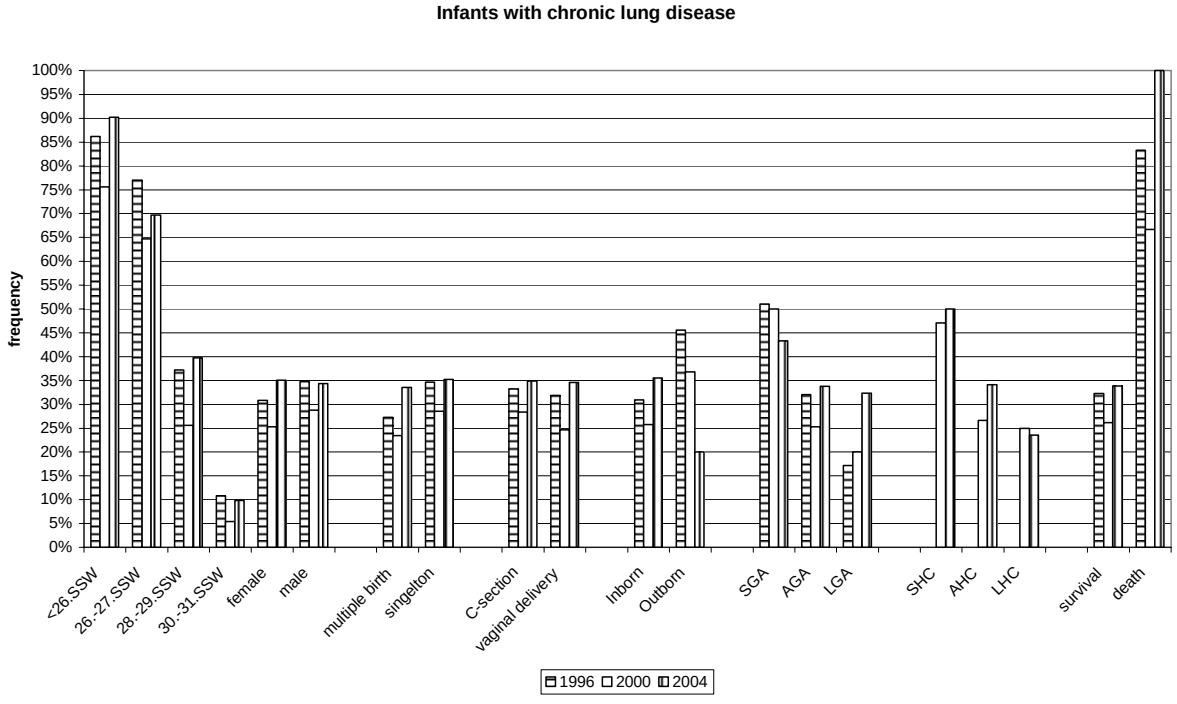
The following analysis only based on the infants who survived the 28th day or were dismissed to home before the 28th day. Therefore the neonatal deaths - 65 children in 1996, 83 in 2000 and 65 in 2004 - were excluded.

4.4.7.1 Description

The incidence of chronic lung disease (CLD) varied significantly (p_C=0.016) between 32.9% in 1996, 27.0% in 2000, 34.7% in 2000, and on average 31.5% (95% CI 29.2-33.8%). The minimal rate of infants with a CLD was 22.2% in 1996, 10.3% in 2000, 19.3% in 2004, and on average 23.9%. The maximal rates were 39.6% in 1996, 50.0% in 2000, 47.6% in 2004, and on average 40.3%.

The average frequency of infants with a chronic lung disease decreased with increasing gestational age (Figure 20) with the exception of the youngest age group: 83.8% of the infants with <26 completed gestational weeks had on average a CLD, 69.8% of the ones with 26-27 weeks, 34.2% of the ones with 28 and 29 weeks and 8.7% of the ones with 30-31 weeks. Any two age groups differed significantly (p_C=0.005 between infants with <26 weeks and infants with 26-27 weeks, p_C <0.001 all other pairs of age groups differed significantly).
The incidence of CLD for the infants with <26 weeks tended to remain stable over the years and varied between 86.2% in 1996, 75.6% in 2000 and 90.2% in 2004 (p_C=0.18). The rate of infants with 26-27 weeks varied not significantly either between 77.0% in 1996, 64.7% in 2000 and 69.4% in 2004 (p_C=0.21). 37.2% of the infants with 28-29 weeks had a CLD in 1996, 25.6% in 2000 and 39.8% in 2004; the rates differed significantly over the years (p_C=0.018). The incidence of the oldest age group varied inconsiderably (p_C=0.07) between 10.8% in 1996 and 5.4% in 2000 respectively 9.8% in 2004 although the change between 1996 and 2000 was significantly (p_C=0.025).

Figure 20: Distribution of infants with chronic lung disease per different categories and per year.



The frequency of females with a chronic lung disease amounted to 30.8% in 1996, 25.3% in 2000, 35.1% in 2004, and on average 30.3%. The differences over the years were significantly (p_C=0.044). The incidence of males tended to remain stable (p_C=0.24) in the range of 34.7% in 1996, 28.8% in 2000 and 34.4% in 2004 with the average rate of 32.6%. No significant difference could be observed between the gender in any year and overall (p_C=0.35 in 1996 and in 2000, p_C=0.86 in 2004, p_C=0.33 overall; female versus male OR=0.90, 95% CI 0.73-1.11).

The incidence of a CLD for multiple births didn't vary significantly (p_C=0.11) between 27.3% in 1996, 23.5% in 2000 and 33.5% in 2004 and the average rate was 28.4% although the change between 2000 and 2004 was significantly (p_C=0.049). A similar result was obtained for single births: a non-significant (p_C=0.08) variation between 34.6% in 1996, 28.5% in 2000 and 35.2% in 2004, an average rate of 32.7% and a significant change between 2000 and 2004 (p_C=0.043). The rates didn't differ significantly between single and multiple births in any year and overall (p_C=0.13 in 1996, p_C=0.22 in 2000, p_C=0.63 in 2004, p_C=0.08 overall; multiple versus single births OR=0.81, 95% CI 0.64-1.03).

33.2% of the infants born by C-section had a chronic lung disease in 1996, 28.4% in 2000, 34.9% in 2004, and on average 32.1%. The incidences didn't differ significantly over the years (p_C=0.11) but the yearly change between 2000 and 2004 was significantly (p_C=0.041). The incidence of vaginal born children tended to remain stable (p_C=0.20): 31.9% in 1996, 24.6% in 2000, 34.6% in 2004, and on average 30.5%. The frequencies didn't differ significantly between infants born by C-section and vaginal births in any year and overall (p_C=0.77 in 1996, p_C=0.40 in 2000, p_C=1.00 in 2004, p_C=0.54 overall; C-section versus vaginal births OR=1.08, 95% CI 0.85-1.38).

The rate of inborns with CLD amounted to 30.9% in 1996, 25.8% in 2000, 35.5% in 2004, and on average 30.9%. The incidences differed significantly over the years (p_C=0.033). The incidence of outborns tended to decrease (p_C=0.05, p_L=0.018) significantly from 45.6% in 1996 to 36.8% in 2000 and 20.0% in 2004 with an average rate of 37.3%. The rates differed significantly between inborns and outborns only in 1996 (p_C=0.017 in 1996, p_C=0.06 in 2000, p_C=0.08 in 2004, p_C=0.08 overall; inborns versus outborns OR=0.75, 95% CI 0.54-1.04).

The frequency of SGA infants with chronic lung disease tended to decrease (p_C=0.77) from 51.1% in 1996 to 50.0% in 2000 and 43.3% in 2004. The incidence of AGA children differed significantly (p_C=0.011) between 32.0% in 1996, 25.3% in 2000 and 33.8% in 2004. The LGA infants had an increasing trend (p_C=0.28) of CLD from 17.1% in 1996 to 20.0% in 2000 and 32.4% in 2004. SGA and AGA infants had a significant difference occurrence of CLD in 1996 and 2000 (p_C=0.009 in 1996, p_C<0.001 in 2000, p_C=0.14 in 2004). The difference between SGA and LGA children was significantly in 1996 and 2000 as well (p_C=0.002 in 1996, p_C=0.005 in 2000, p_C=0.29 in 2004). AGA and LGA infants with CLD didn't differ significantly (p_C=0.07 in 1996, p_C=0.49 in 2000, p_C=0.88 in 2004).
The average rate of CLD was 47.7% of the SGA, 30.3% of the AGA and 23.1% of the LGA children. The SGA infants had a doubled risk relative to the AGA ones to have a CLD (p_C<0.001; OR=2.11, 95% CI 1.51-2.95). AGA and LGA infants had no significant difference (p_C=0.12, OR=0.69, 95% CI 0.43-1.11). The AGA children had a lower risk relative to the rest of the infants to have a CLD (p_C=0.016; LGA versus AGA OR=0.71, 95% CI 0.54-0.94).

The incidence of CLD for SHC infants tended to increase from 47.1% in 2000 to 50.0% in 2004 (p_C=0.80), an average rate of 48.7%. A significant increase from 26.6% to 34.1% was observed for AHC children (p_C=0.013) with an average frequency of 30.4%. The rate of LHC infants with CLD tended to remain stable between 25.0% in 2000 and 23.5% in 2004 (p_C=0.88) and the average rate amounted to 24.4%. All rates of SHC with CLD differed significantly from the rates of AHC (p_C<0.001; OR=2.17, 95% CI 1.36-3.46). The incidences of CLD for AHC and LHC didn't differ significantly (p_C=0.25; LHC versus AHC OR=0.74, 95% CI 0.44-1.24).

32.3% of the surviving infants were diagnosed with a chronic lung disease in 1996, 26.2% in 2000, 33.9% in 2004, and on average 30.7%. The rates varied significantly over the years (p_C=0.014). The incidence of infants who died during their stay in a perinatal centre amounted to 83.3% in 1996, 66.7% in 2000, 100.0% in 2004, and on average 80.0% - no significant increase (p_C=0.21).

4.4.7.2 Mortality rate

The mortality rate of the infants with a chronic lung disease tended to remain stable (p_C=0.55) in the range between 3.0% in 1996, 5.3% in 2000 and 3.1% in 2004 with an average rate of 3.7% (95% CI 2.2-5.6%). 0.3% of the infants who didn't have a CLD died in 1996, 1.0% in 2000 and no infant in 2004, an average rate of 0.4% (95% CI 0.1-0.8%). The mortality rates of the children without a CLD didn't differ significantly over the years (p_C=0.11). Obviously, the rates differed significantly in all years and overall (p_C=0.009 in 1996, p_C=0.002 in 2000, p_C <0.001 in 2004 and overall). The infants with a CLD had a 8.5 times higher risk to die than the ones without a CLD (OR=8.56, 95% CI 3.18-23.05).

4.4.8 Bronchopulmonary dysplasia

The following analysis based only on the infants who completed the 36 weeks' postmenstrual age (PMA) or were dismissed to home before they reached the 36 weeks' PMA. Therefore 66 children in 1996, 92 in 2000 and 71 in 2004 were excluded.

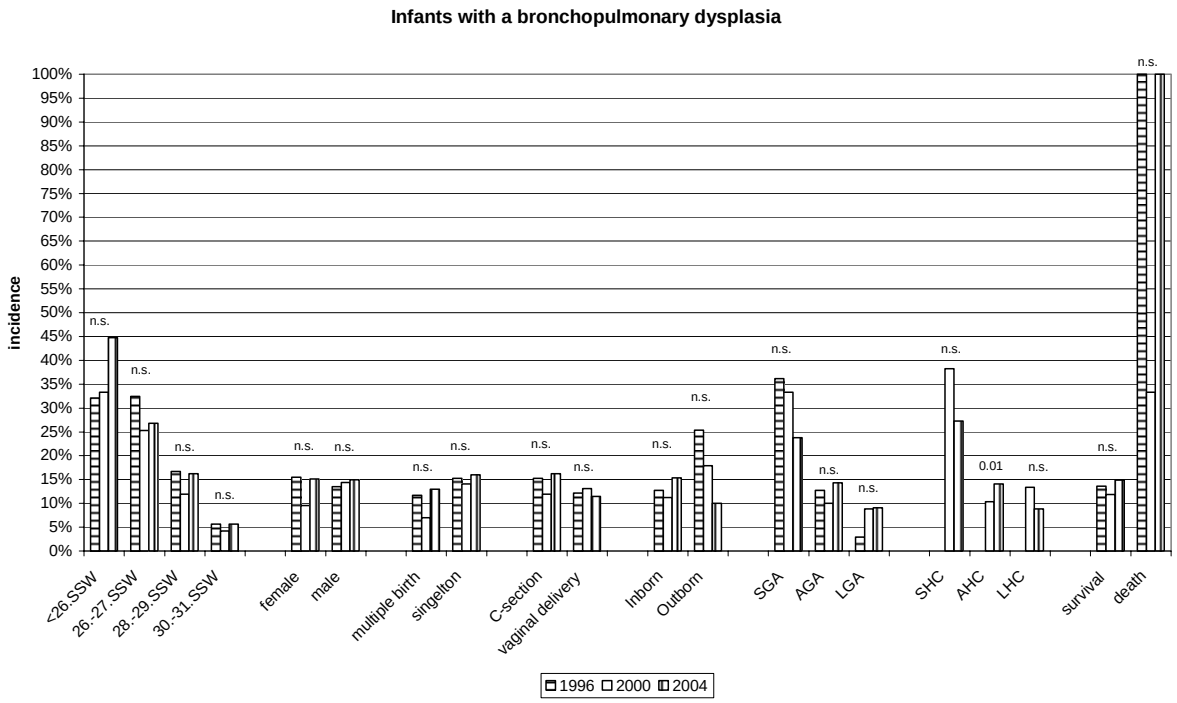
4.4.8.1 Description

The frequency of infants with BPD tended to remain stable (p_C=0.31) and was 14.4% in 1996, 12.0% in 2000, 15.0% in 2000, and on average 13.8% (95% CI 12.1-15.5%). The minimal rate of infants with a BPD was 8.3% in 1996, 2.2% in 2000, 4.9% in 2004, and on average 7.5%. The maximal rates were 23.1% in 1996, 22.2% in 2000, 31.3% in 2004, and on average 21.1%.

The incidence of BPD for infants with <26 completed gestational weeks was 32.1% in 1996, 33.3% in 2000 and 44.7% in 2004 (Figure 21). The rates didn't vary significantly over the years (p_C=0.49). No significant differences between the years could be observed for the other age groups either. 32.4% of the infants with 26 and 27 weeks had a BPD in 1996, 25.3% in 2000 and 26.8% in 2004 (p_C=0.56). The frequency for infants with 28 and 29 weeks with BPD amounted to 16.7% in 1996, 11.9% in 2000 and 16.3% in 2004 (p_C=0.43). 5.6% of the infants with 30 and 31 weeks had a BPD in 1996, 4.2% in 2000 and 5.7% in 2004 (p_C=0.70). The incidence of bronchopulmonary dysplasia decreased with increasing gestational age with an exception of the youngest age group. The average rate was 37.4% for the infants with <26 weeks, 27.8% for the ones with 26 and 27 weeks, 14.9% for the ones with 28 and 29 weeks and 5.2% for the ones with 30 and 31 weeks (p_C=0.08 between infants with <26 weeks and the ones with 26-27 weeks, p_C<0.001 for all other pair of age groups).

15.5% of the females had a BPD in 1996, 9.6% in 2000 and 15.1% in 2004. The rates didn't vary significantly over the years (p_C=0.08). The average frequency was 13.3%. The incidence of the males tended to increase (p_C=0.89, p_L=0.63) from 13.5% in 1996 to 14.4% in 2000 and 14.9% in 2004 with an average rate of 14.3%. The frequencies didn't differ significantly between females and males (p_C=0.51 in 1996, p_C=0.08 in 2000, p_C=0.97 in 2004, p_C=0.56 overall; females versus males OR=0.92, 95% CI 0.69-1.22).
The incidence of BPD for multiple births didn't vary significantly (p_C=0.18) between 11.7% in 1996, 7.0% in 2000 and 12.9% in 2004. The average rate amounted to 10.5%. The frequency of single births with BPD tended to remain stable (p_C=0.74) and was 15.3% in 1996, 14.0% in 2000, 16.0% in 2004, and on average 15.1%. The frequencies differed significantly between the two groups in 2000 (p_C=0.31 in 1996, p_C=0.020 in 2000, p_C=0.43 in 2004). The overall risk of multiple births relative to the singletons were significantly lower than one (p_C=0.016, OR=0.66, 95% CI 0.47-0.93).

Figure 21: Distribution of infants who were alive at 36 weeks' PMA with chronic lung disease per different categories and per year.



15.3% of the infants born by C-section had a BPD in 1996, 12.0% in 2000, 16.2% in 2004, and on average 14.5%; no significant different rates (p_C=0.19). For vaginal born children, the frequency of children with BPD tended to remain stable (p_C=0.92): 12.1% in 1996, 13.1% in 2000, 11.5% in 2004, and on average 12.2%. The two groups didn't differ in the incidence in any year and overall (p_C=0.37 in 1996, p_C=0.73 in 2000, p_C=0.17 in 2004, p_C=0.25 overall; C-section versus vaginal births OR=1.22, 95% CI 0.86-1.71).

The rate of inborns with BPD was 12.8% in 1996, 11.2% in 2000, 15.3% in 2004, on average 13.2%. The incidences didn't vary over the years (p_C=0.15) although there was a significant yearly change between 2000 and 2004 (p_C=0.048). The frequency of outborns with BPD tended to decrease (p_C=0.19, p_L=0.07) from 25.4% in 1996 to 17.9% in 2000 and 10.0% in 2004 with an average rate of 19.5%. A significant different incidence between the two groups could be observed in 1996 (p_C=0.006 in 1996, p_C=0.12 in 2000, p_C=0.43 in 2004). The odds ratio of the inborns relative to the outborns amounted to 0.63 (p_C=0.027, 95% CI 0.41-0.95).

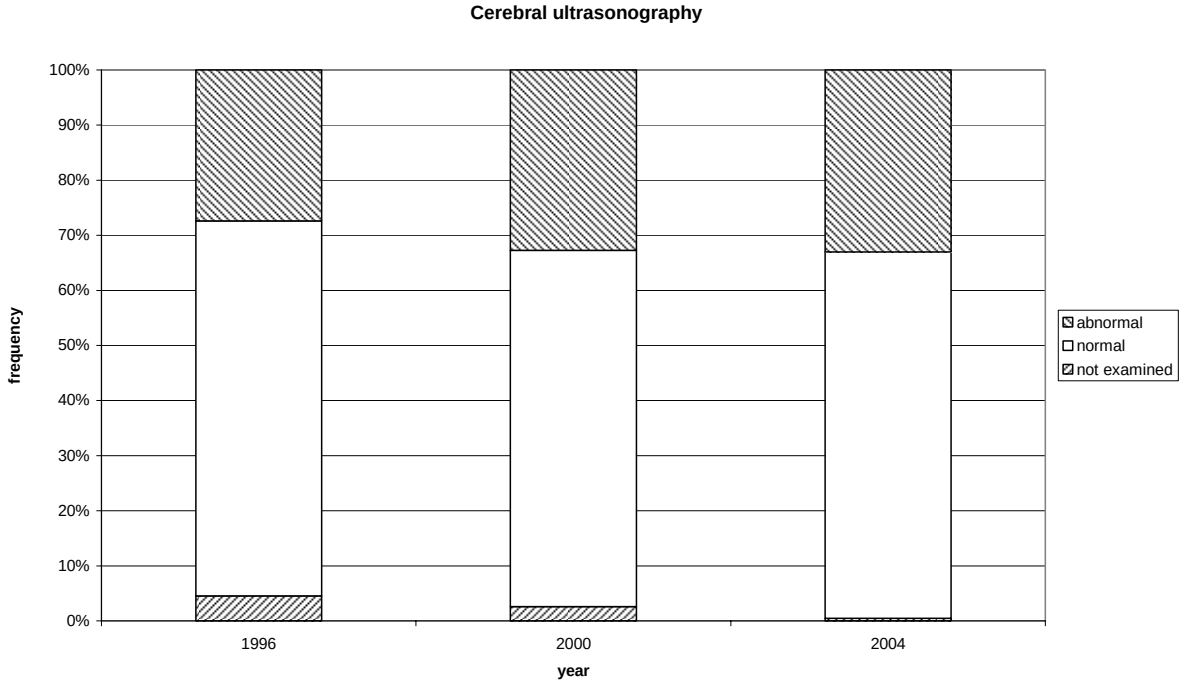
The frequency of SGA infants with BPD tended to decrease (p_C=0.34, p_L=0.16) from 36.2% in 1996 to 33.3% in 2000 and 23.7% in 2004. 12.7% of the AGA children were diagnosed with BPD in 1996, 10.0% in 2000 and 14.3% in 2004 The increase from 2000 to 2004 was significantly (p_C=0.046) although the rates didn't vary significantly over the years (p_C=0.13).The incidence of LGA infants tended to increase (p_C=0.53, p_L=0.32) from 2.9% in 1996 to 8.8% in 2000 and 9.1% in 2004.
The average rate was 30.5% for SGA, 12.4% for AGA respectively 6.9% for LGA infants. The incidence of SGA children was significantly higher than the one for AGA in all years and overall (p_C <0.001 in 1996 and 2000 and overall, p_C=0.031 in 2004; SGA versus AGA OR=3.11, 95% CI 2.13-4.55). The AGA and LGA infants didn't differ significantly in the occurrence of BPD in any year and overall (p_C=0.08 in 1996, p_C=0.81 in 2000, p_C=0.41 in 2004, p_C=0.10 overall, LGA versus AGA OR=0.53, 95% CI 0.24-1.16). The risk of AGA children was almost half of the one of the rest of the infants (p_C<0.001, OR=0.53, 95% CI 0.37-0.74).

The incidence of BPD for SHC infants tended to decrease from 38.2% in 2000 to 27.3% in 2004 (p_C=0.30) with an average rate of 32.1%. The rate of LHC ones with BPD showed a decreasing trend (p_C=0.08) as well: 10.4% in 2000, 14.1% in 2004 and on 12.3%. The frequency of AHC ones with BPD tended to increase (p_C=0.53) from 13.3% in 2000 to 8.8% and the average rate was 11.4%.
The SHC infants had a significant higher frequency of BPD than the AHC in 2000, 2004 and overall (p_C <0.001 in 2000 and overall, p_C=0.02 in 2004) respectively LHC ones (p_C=0.011 in 2000, p_C=0.042 in 2004, p_C=0.002 overall). The SHC ones had more than a three times higher risk to have a BPD than the AHC ones (OR=3.37, 95% CI 2.02-5.64). The difference of the rates between AHC and LHC children wasn't significantly in any year and overall (p_C=0.54 in 2000, p_C=0.38 in 2004, p_C=0.80 overall; LHC versus AHC OR=0.92, 95% CI 0.45-1.89). The AHC infants had half the risk than the rest of the children (OR=0.51, 95% CI 0.33-0.78).
The frequency of survivors with BPD tended to remain stable over the years (p_C=0.34): 13.6% in 1996, 11.9% in 2000, 14.9% in 2004, and on average 13.4%. The incidence of BPD for the infants who died during the stay in a perinatal centre differed inconsiderably over the years (p_C=0.08) and amounted to 100% (5 infants) in 1996, 33.3% (1 infant) in 2000, 100% (1 infants) in 2004, and on average 77.8%.

4.4.8.2 Mortality rate

The mortality rate of the infants with a bronchopulmonary dysplasia amounted to 6.8% in 1996, 1.5% in 2000 and 1.2% in 2004, an average rate of 3.1% (95% CI 0.6-1.8%), only a linear significant difference (p_C=0.54, p_L=0.047). None of the infants who didn't have a BPD died in 1996 and 2004, 0.4% (2 infants) in 2000 and an average rate of 0.1% (95% CI 1.1-6.0%); no significant difference over the years (p_C=0.15). The rates differed significantly in 2000, 2004 and overall (p_C<0.001 in 1996, p_C=0.31 in 2000, p_C=0.020 in 2004, p_C<0.001 overall). Due to the low number, the infants with a BPD had an about 22 times higher risk to die than the ones without a BPD (OR=22.52, 95% CI 4.65-109.13)

Figure 22: Incidence of a cerebral ultrasound per year.



4.4.9 Cerebral ultrasound examination

The portion of the infants who didn't get a cerebral ultrasonography (Figure 22) decreased from 4.5% in 1996 to 2.6% in 2000 and 0.5% in 2004 with an average rate of 2.5%. A stable frequency of the infants with a normal cerebral ultrasound finding varied between 68.1% in 1996, 64.7% in 2000 and 66.5% in 2004. The average rate amounted to 66.4%. The rate of an abnormal findings tended to increase from 27.4% in 1996 to 32.7% in 2000 and 33.0% in 2004. 31.2% of the infants had on average an abnormal finding. However none of the temporal developments were significant.

4.4.10 Intracranial haemorrhage

4.4.10.1 Description

The diagnosis of an intracranial haemorrhage (Figure 23) was made only for a small percentage of the children who were delivered to the perinatal centres and were examined by cerebral ultrasonography - 573 infants in 1996, 645 in 2000 and 551 in 2004. No haemorrhage was observed for 76.8% of the infants in 1996, 72.2% in 2000 and 76.0% in 2004. The rates between didn't vary significantly over the years (p_C=0.14).

On average, 12.4% of the infants had grade 1, 4.8% grade 2, 1.9% grade 3 and 6.0% grade 4. The incidence of grade 3 and 4 tended to increase (p_C=0.68, p_L=0.39) from 7.3% in 1996 to 7.8% in 2000, and to 8.7% in 2004, and on average 7.9% (95% CI 6.7-9.2%) Only the grades 3 and 4 are analysed in the rest of this chapter.
The variability of an intracranial haemorrhage grade 3-4 within the perinatal centres varied over time. There was one perinatal centre who reported no intracranial haemorrhage in 1996. In the other years, the minimal incidence amounted to 4.0% in 2000, and 2.0% in 2004, and on average 3.4%. The maximal frequency in one of the perinatal centres amounted to 19.5% in 1996, 15.0% in 2000, 15.4% in 2004, and on average 13.0%.

The frequency of an intracranial haemorrhage grade 3 or 4 (Figure 24) decreased with increasing gestational age: 19.8% of the infants with <26 completed gestational age had on average were reported to have a grade 3 or 4, 14.3% of the infants with 26 and 27 weeks, 8.5% of the children with 28 and 29 weeks and 2.0% of the ones with 30 and 31 weeks. The only non-significant difference could be found between the smallest two age groups (p_C=0.10 between infants with <26 weeks and 26-27 weeks), all other two age groups differed significantly (p_C <0.001 between infants with <26 weeks and infants with 28-29 weeks respectively 30-31 weeks, p_C=0.004 between infants with 26 and 27 weeks and infants with 28-29 weeks, p_C<0.001 between infants with 26-27 weeks and infants 30-31 weeks respectively between infants with 28-29 weeks and infants with 30-31 weeks).

The incidence of children with <26 completed weeks and an intracranial haemorrhage grade 3 or 4 decreased from 33.9% in 1996 to 11.8% in 2000 respectively 16.4% in 2004 (p_C=0.005). 7.5% of the infants with 26-27 completed weeks had an intracranial haemorrhage grade 3 or 4 in 1996, 14.0% in 2000 and 20.6% in 2004. The decrease was significantly as well (p_C=0.031, p_L=0.009). For the infants with 28-29 completed weeks, the increase from 7.2% in 1996 to 9.2% in 2000 respectively 9.0% in 2004 wasn't significantly (p_C=0.76). Also no significant change (p_C=0.62) was found for the infants with 30-31 completed weeks: 1.6% in 1996 respectively 2004 and 2.6% in 2000.

6.7% of the female infants had an intracranial haemorrhage grade 3 or 4 in 1996 and 2004, 8.2% in 2000, and on average 7.3%. The changes weren't significantly (p_C=0.72). The incidence of male children was 7.8% in 1996, 7.3% in 2000, 10.4% in 2004, and on average 8.5%, no significant changes (p_C=0.33). The rates didn't differ significantly either between female and male infants in any year and overall (p=0.61 in 1996, p=0.66 in 2000, p=0.12 in 2004, p=0.36 overall; female versus male OR=0.85, 95% CI 0.6-1.2).

Figure 23: Incidence of intracranial haemorrhage per year.

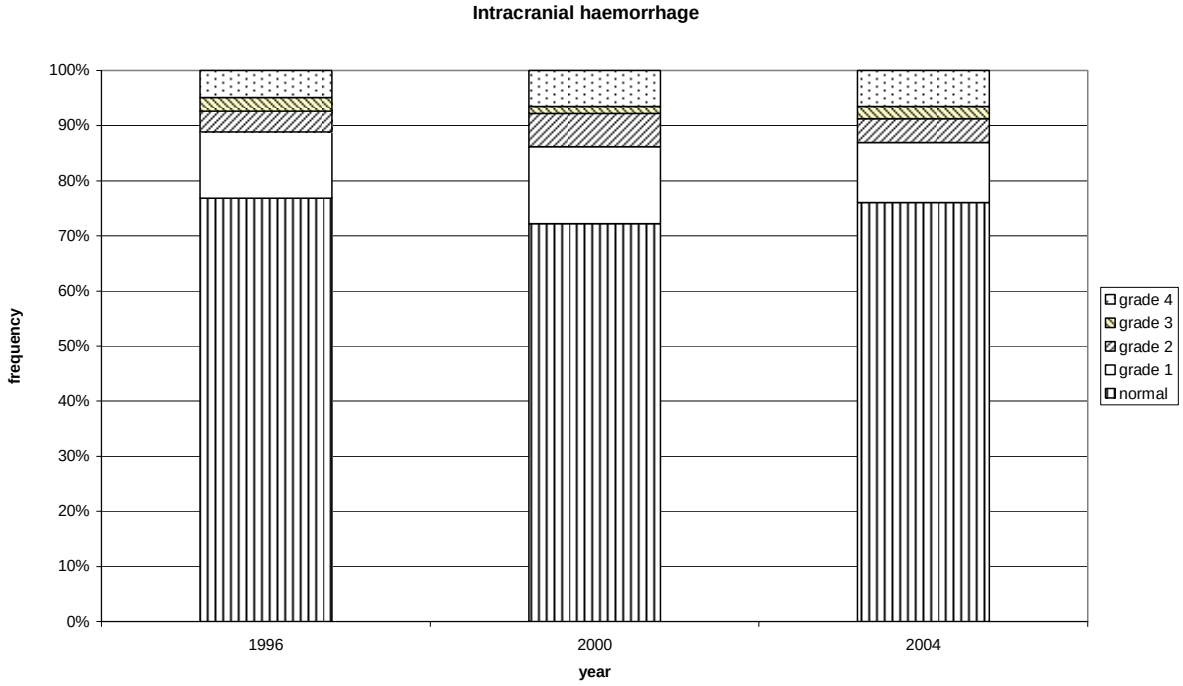
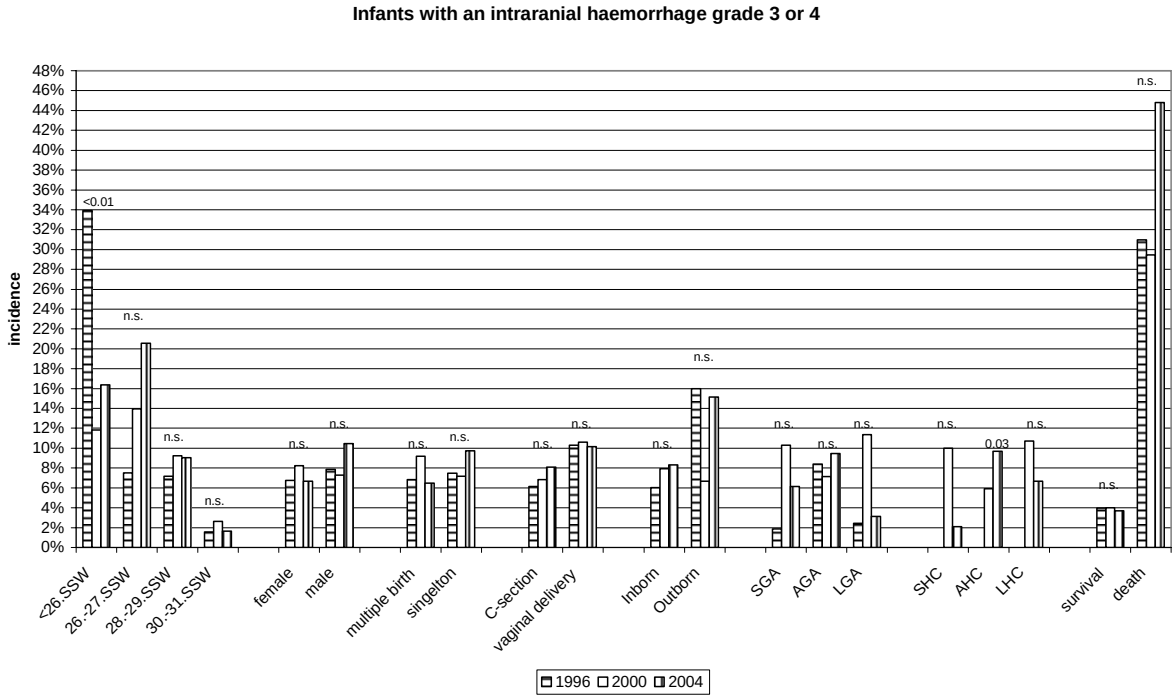


Figure 24: Distribution of infants with an intracranial haemorrhage grade 3 or 4 per different categories and per year.



A similar result as for the gender was observed for the mode of delivery. The rate of multiple birth infants with an intracranial haemorrhage grade 3 or 4 was 6.8% in 1996, 9.2% in 2000, 6.5% in 2004, and on average 7.6% significantly (p_C=0.58). 7.5% of the single birth children had an intracranial haemorrhage grade 3 or 4 in 1996, 7.2% in 2000, 9.7% in 2004, and on average 8.0% significantly (p_C=0.35). No significant different rates between single and multiple birth children can be observed in any year or overall (p_C=0.79 in 1996, p_C=0.38 in 2000, p_C=0.21 in 2004, p_C=0.77 overall; multiple versus single birth OR=0.94, 95% CI 0.64-.139).

The incidence of infants born by C-section who had an intracranial haemorrhage grade 3 or 4 tended to increase (p_C=0.54, p_L=0.27) from 6.1% in 1996 to 6.8% in 2000 respectively 8.1% in 2004, on average 7.0%. The rate for vaginal delivered infants remained stable (p_C=0.99) in the range of 10.3% in 1996, 10.6% in 2000 and 10.2% in 2004, on average 10.4%. The frequency differed significantly between vaginal delivered infants and the ones delivered by C-section only overall (p_C=0.08 in 1996, p_C=0.13 in 2000, p_C=0.47 in 2004, p_C=0.024 overall). The relative risk of children born by C-section to have an intracranial haemorrhage grade 3 or 4 was significantly lower than one (OR=0.65, 95% CI 0.45-0.95).

The rates of inborns with an intracranial haemorrhage grade 3 or 4 tended to increase (p_C=0.33, p_L=0.17) from 6.0% in 1996 to 7.9% in 2000 and 8.3% in 2004, on average 7.4%. The frequencies for outborns tended to remain stable (p_C=0.18): 16.0% in 1996, 6.7% in 2000, 15.2% in 2004, and on average 12.0%. The incidence differed significantly in 1996 and overall (p_C=0.002 in 1996, p_C=0.71 in 2000, p_C=0.18 in 2004, p_C=0.030 overall). Inborns had significantly more seldom an intracranial haemorrhage grade 3 or 4 relative to outborns (OR=0.59, 95% CI 0.36-0.96).

The incidence of SGA infants with an intracranial haemorrhage grade 3 or 4 didn't differ significantly (p_C=0.17) between the years: 1.9% in 1996, 10.3% in 2000 and 6.2% in 2004. The rates tended to remain stable (p_C=0.41) for AGA children: 8.4% in 1996, 7.1% in 2000 and 9.5% in 2004. 2.4% of the LGA infants had an intracranial haemorrhage grade 3 or 4 in 1996, 11.4% in 2000 and 3.1% in 2004 and the rates didn't vary significantly over the years (p_C=0.16).
The average rate amounted to 6.4% for the SGA, 8.3% for the AGA and 6.0% for the LGA infants. The SGA and the AGA infants didn't have a different risk of intracranial haemorrhage grade 3 and 4 (p_C=0.09 in 1996, p_C=0.35 in 2000, p_C=0.38 in 2004, p_C=0.38 overall; OR=0.76, 95% CI 0.41-1.41). The same is true for LGA versus AGA children (p_C=0.88 in 1996, p_C=0.85 in 2000, p_C=0.55 in 2004, p_C=0.88 overall; OR=0.71, 95% CI 0.32-1.55). The odds ratio of the AGA children relative to the rest of the infants amounted overall to 1.35 (p_C=0.23, 95% CI 0.82-2.23).

10.0% of the SHC infants had an intracranial haemorrhage grade 3 or 4 in 2000, 2.1% in 2004, and on average 6.1%; no significant change (p_C=0.10). The incidence increased significantly (p_C=0.027) for the AHC children from 5.9% in 2000 to 9.7% in 2004; the average rate was 7.7%. The rate for the LHC infants tended to decrease (p_C=0.54) from 10.7% in 2000 to 6.7% in 2004 with an average rate of 7.7%.
No significant differences between any two groups were found in any year and overall. The relative risk of SHC infants to have an intracranial haemorrhage grade 3 or 4 wasn't significantly different lower than one relative to the AHC ones (p_C=0.24 in 2000, p_C=0.08 in 2004, p_C=0.57 overall; OR=0.78, 95% CI 0.33-1.84). The risk for the LHC children wasn't significantly higher than one relative to the AHC ones (p_C=0.90 in 2000, p_C=0.34 in 2004, p_C=0.40 overall; OR=1.23, 95% CI 0.57-2.63). The odds ratio of the AHC infants relative to the rest of the children amounted to 1.02 (p_C=0.95, 95% CI 0.56-1.84).

The surviving infants with an intracranial haemorrhage grade 3 or 4 tended to remain on a stable level (p_C=0.97): 4.0% in 1996 and 2000, 3.7% in 2004, and on average 3.9%. 31.0% of the children who died in the perinatal centres had an intracranial haemorrhage grade 3 or 4 in 1996, 29.5% in 2000, 44.8% in 2004, and on average 34.3%. The rates didn't vary significantly over the years (p_C=0.10) although the change between 2000 and 2004 was significantly (p_C=0.046 between 2000 and 2004).

4.4.10.2 Mortality rate

The average mortality rate of the infants increased with the grade of the intracranial haemorrhage: 6.4% for grade 1 (95% CI 3.1-9.7%), 21.2% for grade 2 (95% CI 12.3-30.0%), 26.5% for grade 3 (95% CI 10.8%-42.1%) and 67.0% for grade 4 (95% CI 57.9%-76.1%). The only non-significant

difference could be found between grade 2 and 3 (p_C=0.53), all other two different intracranial haemorrhage grades were significantly (p_C <0.001 for all pairs). 9.1% of the infants (95% CI 7.6-10.7%) who died in the perinatal centre didn't have an intracranial haemorrhage. This rate differed significantly with the infants who had an intracranial haemorrhage with grade higher than 1 (p_C=0.19 for grade 1, p_C <0.001 for grade >1). The mortality rates didn't vary significantly over the years for any grades of the intracranial haemorrhage except grade 3 (grade 1 p_C=0.20, grade 2 p_C=0.44, grade 3 p_C=0.011, grade 4 p_C=0.25) and for the infants without an intracranial haemorrhage (p_C=0.31).
The mortality rate for infants with no or an intracranial haemorrhage grade <3 amounted to 9.2% in 1996, 11.3% in 2000, 7.4% in 2004, and on average 9.4% (95% CI 8.0-10.8%). The rates didn't vary significantly over the years (p_C=0.09) however the difference between 2000 and 2004 was significantly (p_C=0.028 between 2000 and 2004). The mortality rate for infants with an intracranial haemorrhage grade 3 or 4 tended to increase (p_C=0.61) from 52.4% in 1996 to 56.0% in 2000 and 62.5% in 2004 (p=0.74 between 1996 and 2000, p=0.51 between 2000 and 2004, p=0.33 between 1996 and 2004); the average rate was 57.1% (95% CI 48.8%-65.4%).

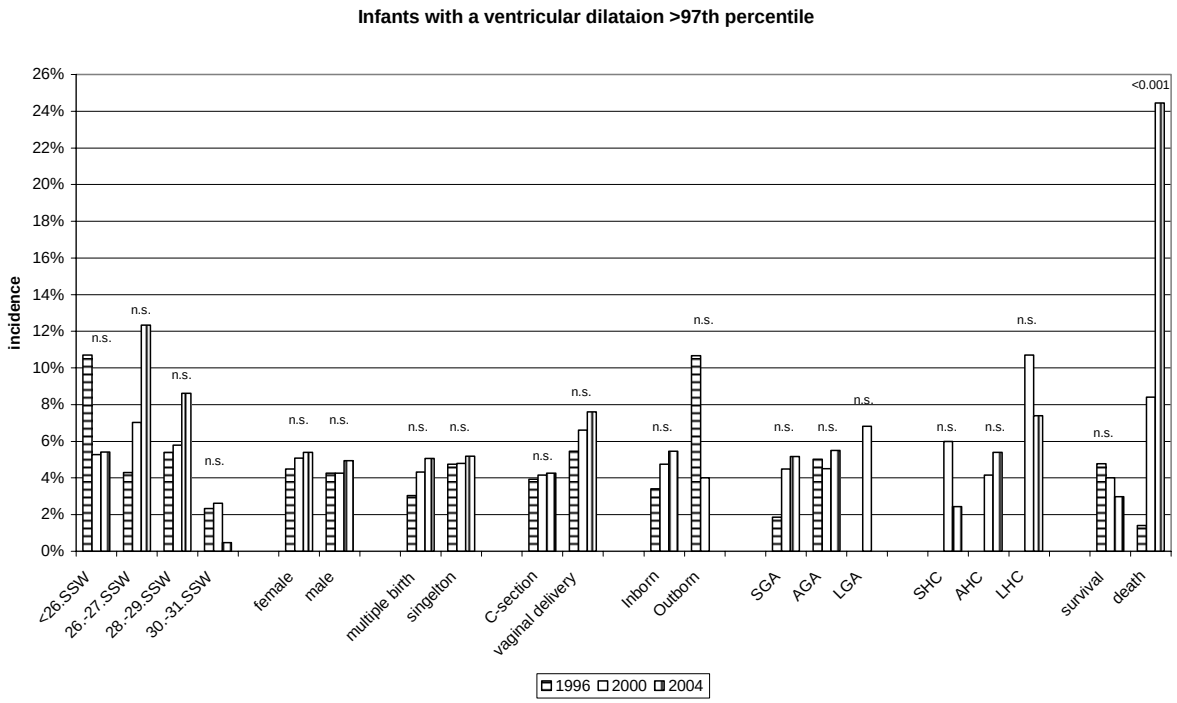
4.4.11 Ventricular dilatation

4.4.11.1 Description

Analysing the 1664 infants - 573 in 1996, 644 in 2000 and 447 in 2004 - with an information about the ventricles, the frequency of children with a normal ventricular size tended to remain stable over time: 95.6% in 1996, 95.3% in 2000, 94.9% in 2004, and on average 95.3%. 3.1% of the infants had a ventricular dilatation 1-4mm above >97th percentile in 1996, 2.5% in 2000, 4.0% in 2004, and on average 3.1%. The incidence of infants with ventricular dilatation >4mm above 97th percentile was 1.2% in 1996, 2.2% in 2000, 1.1% in 2004, and on average 1.6%.
Therefore the infant with a ventricular size >97th percentile tended to increase not significantly (p_C=0.84, p_L=0.56) from 4.4% in 1996 to 4.7% in 2000 and 5.1% in 2004. On average the incidence of a ventricular dilatation was 4.7% (95% CI 3.7-5.7%).
In 1996, 80% of the children with a ventricular size >97th percentile had an intracranial haemorrhage, 70% in 2000 and 100% in 2004. The changes weren't significantly different (p_C=0.05).
There was a perinatal centre without a child with a ventricular dilatation in 1996 and 2004 and the minimal incidence of infants with ventricular dilatation >97th percentile was 1.6% in 2000, on average 0.7%. The maximal frequency in one of the perinatal centres amounted to 9.8% in 1996, 9.1% in 2000 and 18.9% in 2004, on average 7.9%.

The incidence of ventricular dilatation >97th percentile tended to decrease with gestational age except the smallest age group (Figure 25): the average rate for infants <26 completed weeks was 7.1%, 7.6% for infants with 26-27 weeks, 6.4% for infants with 28-29 weeks and 1.9% for infants with 30-31 weeks. Only the oldest children with 30-31 completed weeks had a significant lower rate than each of the other age groups (p_C<0.001 with each group). The rest of the frequencies didn't differ significantly between any two age groups.
For the infants with <26 completed gestational weeks, the rate of ventricular dilatation amounted to 10.7% in 1996, 5.3% in 2000 and 5.4% in 2004 and the frequencies didn't vary significantly over the years (p_C=0.44). A tendency of increasing incidences was observed for the two middle age groups (p_C=0.13, p_L=0.048): 4.3% of the infants with 26 and 27 completed weeks had a ventricular dilatation >97th percentile in 1996, 7.0% in 2000 and 12.3% in 2004. The incidence of infants with 28-29 weeks remained stable (p_C=0.51) and amounted to 5.4% in 1996, 5.8% in 2000 and 8.6% in 2004. For infants with 30 and 31 weeks, the frequency was 2.3% in 1996, 2.6% in 2000 and 0.5% in 2004, no significant differences over the years as well (p_C=0.19).

Figure 25: Distribution of infants with ventricular dilatation >97th percentile per different categories and per year



The incidence of ventricular dilatation >97th percentile tended to increase (females p_C=0.90, males p_C=0.91 and p_{CL}=0.71) over the years for females and males. The rate was 4.5% of the females in 1996, 5.1% in 2000, 5.4% in 2004, and on average 5.0%. 4.2% of the males had a ventricular dilatation >97th percentile in 1996, 4.3% in 2000, 4.9% in 2004, and on average 4.4%. No significant difference between males and females could be shown for any year and overall (p_C=0.87 in 1996, p_C=0.63 in 2000, p_C=0.83 in 2004, p_C=0.61 overall; females versus males OR=1.12, 95% CI 0.71-1.77).

A tendency of increasing rate of ventricular dilatation >97th percentile can be observed for single and multiple births (multiple births p_C=0.70, singletons p_C=0.96 and p_L=0.81): 4.8% of the single birth in 1996 and 2000, 5.2% in 2004, and on average 4.9% respectively 3.0% of the multiple birth in 1996, 4.3% in 2000, 5.1% in 2004, and on average 4.2%. The incidence didn't differ significantly between single and multiple births in any year and overall (p_C=0.38 in 1996, p_C=0.80 in 2000, p_C=0.96 in 2004, p_C=0.55 overall; multiple versus single births OR=0.85, 95% CI 0.50-1.44).

Also the infants born by C-section and the vaginal delivered infants tended to have an increasing frequency of ventricular dilatation >97th percentile. 3.9% of the infants born by C-section had an abnormal ventricular size in 1996, 4.1% in 2000, 4.2% in 2006, and on average 4.1%; no significant differences over the years (p_C=0.97, p_L=0.82). For vaginal delivered infants, the incidence tended to increase (p_C=0.78) from 5.5% in 1996 to 6.6% in 2000 and 6.4% in 2004 (p=0.67 between 1996 and 2000, p_C=0.76 between 2000 and 2004, p_C=0.48 between 1996 and 2004) and the average rate was 6.4%. The frequencies didn't differ significantly between the two difference birth modes in any year and overall (p_C=0.42 in 1996, p_C=0.22 in 2000, p_C=0.18 in 2004, p_C=0.06 overall; C-section versus vaginal births OR=1.59, 95% CI 0.98-2.59).

3.4% of the inborns had a ventricular dilatation >97th percentile in 1996 and the rate tended to increase (p_C=0.31, p_L=0.13) to 4.8% in 2000 and 5.5% in 200. The outborns with an abnormal ventricle size tended to decrease (p_C=0.08, p_L=0.030) from 10.7% in 1996 to 4.0% in 2000 and none in 2004. The average frequency was 4.5% for inborn and 6.3% for outborn infants. The incidence differed

significantly between inborns and outborns only in 1996 (p_C=0.005 in 1996, p_C=0.77 in 2000, p_C=0.23 in 2004, p_C=0.31 overall; inborn versus outborn OR=0.71, 95% CI 0.37-1.37).

The incidence of SGA infants with a ventricular dilatation >97th percentile tended to increase (p_C=0.63, p_L=0.37) from 1.9% to 4.5% in 2000 respectively 5.2% in 2004. The rate tended to remain stable for AGA infants (p_C=0.79): 5.0% in 1996, 4.5% in 2000 and 5.5% in 2004. 6.8% of the LGA children were observed in 2000 with an abnormal ventricular size and none in 1996 and 2004; however the rates didn't vary significantly over the years (p_C=0.10).
On average, 3.9% of the SGA infants had a ventricular dilatation >97th percentile, 4.9% of the AGA and 2.7% of the LGA infants. The SGA children didn't have a significant lower incidence of a ventricular dilatation than the AGA ones (p_C=0.31 in 1996, p_C=1.00 in 2000, p_C=0.90 in 2004, p_C=0.55 overall; OR=0.71, 95% CI 0.35-1.73). The same is true for the LGA children relative to the AGA ones (p=0.41 in 1996, p=0.61 in 2000, p=0.25 in 2004, p=0.60 overall; OR=0.54, 95% CI 0.17-1.74).

6.0% of SHC infants had an abnormal ventricle size in 2000 and this rate didn't decrease significantly (p_C=0.41) to 2.4% in 2004 with an average rate of 4.4%. The incidence tended to increase (p_C=0.39) for AHC children from 4.2% in 2000 to 5.4% in 2004, the average rate was 4.7%. For LHC infants, the rate tended to decrease (p_C=0.63) from 10.7% to 7.4%; on average 9.6%.
The SHC and AHC infants didn't have a significant different rate in any year and overall (p_C=0.56 in 2000, p_C=0.41 in 2004, p_C=0.92 overall; SHC versus AHC OR=0.94, 95% CI 0.33-2.68). The LHC children had an about doubled risk to have a ventricular dilatation than the AHC ones (p_C=0.030 in 2000, p_C=0.66 in 2004, p_C=0.047 overall; OR=2.17, 95% CI 0.98-4.81).

4.4.11.2 Mortality rate

The mortality rate of the infants with a ventricular dilatation > 97th percentile amounted to 4.0% in 1996, 26.7% in 2000 and 62.5% in 2004 (p_C=0.002, p_L<0.001) with an average mortality rate of 26.8% (95% CI 15.7-35.5%). None of the children who had additionally no intracranial haemorrhage died in 1996, 11.1% of the ones in 2000 – the mortality rate isn't defined in 2004 - (p_C=0.44) and on average 7.1%. The mortality rate of the infants who had a ventricular dilatation and an intracranial haemorrhage was 5.0% in 1996, 33.3% in 2000, 62.5% in 2004 (p_C=0.001, p_L<0.001), and on average 31.6%. 12.8% of the children with no ventricular dilatation died in 1996, 14.2% in 2000, 8.0% in 2004 (p_C=0.009), and on average 12.0%.

4.4.12 Periventricular leucomalacia

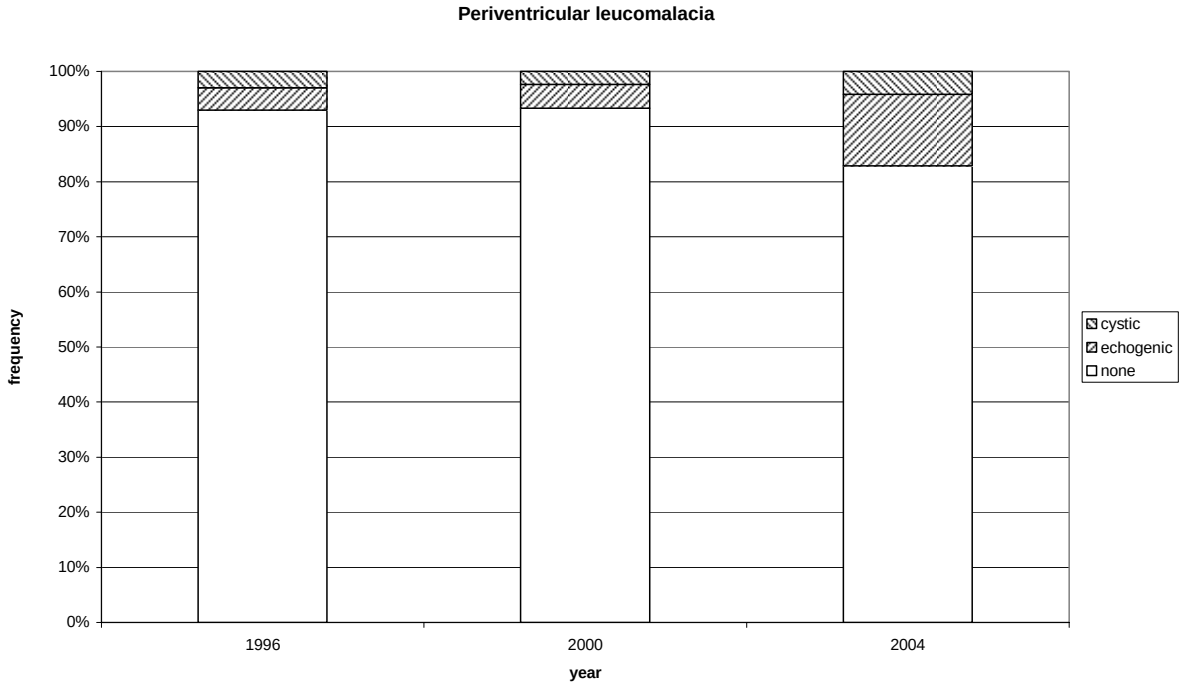
4.4.12.1 Description

The rate of infants with no periventricular leucomalacia decreased significantly (p_C<0.0001) from 93.0% in 1996 respectively 93.3% in 2000 to 82.9% in 2004. The average frequency was 90.1%. The significant change resulted from an increase of the incidence of the infants with echogenic PVL: 4.0% in 1996, 4.4% in 2000, 13.0% in 2004, and on average 6.8% (Figure 26).
The amount of infants with a cystic PVL tended to remain stable (p_C=0.21) over time in the range between 3.0% in 1996, 2.3% in 2000 and 4.1% in 2004 and the average rate was 3.1% (95% CI 2.3-3.9%). The variability of cystic PVL between the perinatal centres increased over time: the maximal rate amounted to 7.1% in 1996, 9.1% in 2000 and 13.7% in 2004.

The rate of cystic PVL tended to decrease with gestational age (Figure 27). The average amount was 4.4% for infants with <26 completed weeks, 3.5% for the ones with 26-27 weeks, 3.0% for the ones with 28-29 weeks and 2.6% for the ones with 30-31 weeks. None of frequencies were significantly between two groups (p_C=0.63 between infants with <26 weeks and the ones with 26-27 weeks, p_C=0.36 between infants with <26 weeks and the ones with 28-29 weeks, p_C=0.19 between infants

with <26 weeks and the ones with 30-31 weeks, p_C=0.68 between infants with 26-27 weeks and the ones with 28-29 weeks, p_C=0.42 between the infants with 26-27 weeks and the ones with 30-31 weeks, p_C=0.72 between infants with 28-29 weeks and the ones with 30-31 weeks).
3.6% of the infants with <26 completed weeks had a cystic PVL in 1996, 1.3% in 2000 and 10.4% in 2004. The rates didn't vary significantly over the years (p_C=0.05) although the change between 2000 and 2004 was significantly (p_C=0.020). The frequency of infants with 26-27 weeks and a cystic PVL tended to remain stable (p_C=0.63) over the years: 4.3% in 1996, 2.3% in 2000 and 4.4% in 2004. No significant changes (p_C=0.76) was found for infants with 28-29 weeks: 3.0% in 1996, 2.3% in 2000 and 3.8%. The rate of infants with 30-31 weeks and cystic PVL amounted to 2.3% in 1996, 2.6% in 2000 and 2.9% in 2004, no significant different rates either (p_C=0.92).

Figure 26: Incidence of periventricular leucomalacia per year.



The incidence of females with a cystic PVL tended to remain stable over time (p_C=0.61): 3.4% in 1996, 3.2% in 2000, 4.7% in 2004, and on average 3.7%. The same result was obtained for the males (p_C=0.26). The rate was 2.6% in 1996, 1.5% in 2000, 3.6% in 2004, and on average 2.5%. No significant differences between females and males were found in any year and overall (p_C=0.41 in 1996, p_C=0.020 in 2000, p_C=0.56 in 2004, p_C=0.17 overall; females versus males OR=1.46, 95% CI 0.84-2.54).

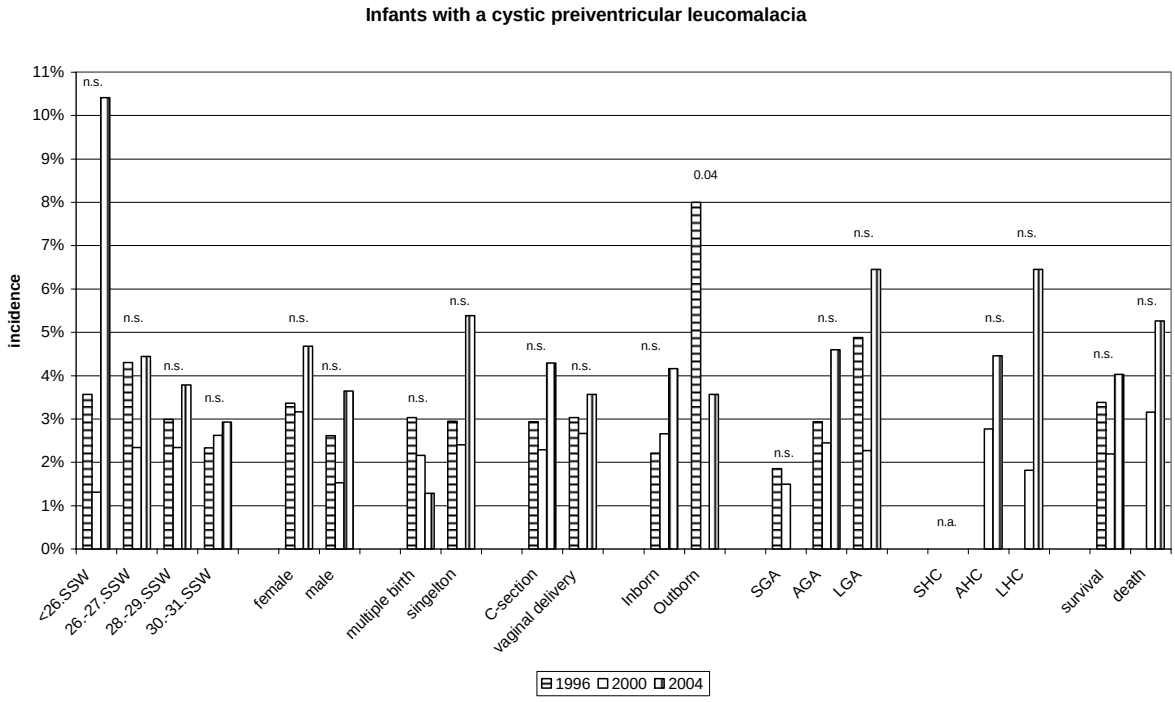
The rate of multiple births with a cystic PVL tended to decrease (p_C=0.59, p_L=0.30) from 3.0% in 1996 to 2.2% in 2000 and 1.3% in 2004 with an average rate of 2.1%. 2.9% of the single births had a cystic PVL in 1996, 2.4% in 2000, 5.4% in 2004, and on average 3.4%. The yearly change between 2000 and 2004 was significantly (p_C=0.027), however the rates didn't differ significantly over the years (p_C=0.05). The frequency of cystic PVL differed significantly only in 2004 (p_C=0.96 in 1996, p_C=0.86 in 2000, p_C=0.033 in 2004, p_C=0.16 overall, multiple versus single births OR=0.61, 95% CI 0.30-1.22).

The incidence of cystic periventricular leucomalacia tended to remain stable for infants born by C-section and vaginal born infants (C-section p_C=0.23, vaginal births p_C=0.91). 2.9% of the infants with infants born by C-section had a cystic PVL in 1996, 2.3% in 2000, 4.3% in 2004, and on average

3.1%. The rate for vaginal born infants was 3.0% in 1996, 2.7% in 2000, 3.6% in 2004, and on average 3.0%. The frequencies didn't differ significantly between the mode of delivery in any year and overall (p_C=0.96 in 1996, p_C=0.81 in 2000, p_C=0.75 in 2004, p_C=0.95 overall; C-section versus vaginal births OR=0.98, 95% CI 0.52-1.85).

The rate of inborns with cystic PVL tended to increase over the years (p_C=0.17, p_L=0.07): 2.2% in 1996, 2.7% in 2000, 4.2% in 2004, and on average 3.0%. 8.0% of the outborns had a cystic PVL in 1996, none in 2000, 3.6% in 2004, and on average 3.9%. The frequencies varied significantly over the years (p_C=0.041). Both groups differed significantly only in 1996 (p_C=0.005 in 1996, p_C=0.15 in 2000, p_C=0.85 in 2004, p_C=0.49 overall). The relative risk of the inborns to have a cystic PVL amounted to 0.75 relative to the outborns (95% CI 0.33-1.69).

Figure 27: Distribution of infants with cystic PVL per different categories and per year.



The frequency of SGA infants with cystic periventricular leucomalacia tended to decrease (p_C=0.57, p_L=0.05) from 1.9% in 1996 to 1.5% in 2000 and no observation in 2004. The rate for AGA children tended to remain stable (p_C=0.16) over the years in the range of 2.9% in 1996, 2.4% in 2000 and 4.6% in 2004. The same result was obtained for LGA (p_C=0.66): 4.9% in 1996, 2.3% in 2000 and 6.5% in 2004.
The incidence was on average 1.1% for the SGA infants, 3.2% for the AGA ones and 4.3% for the LGA ones, no significant differences. The odds ratio of the SGA children relative to the AGA ones amounted to 0.32 (p_C=0.10, 95% CI 0.08-1.35). The LGA infants had a relative risk relative to the AGA ones that wasn't significantly higher than one (p_C=0.51, OR=1.35, 95% CI 0.52-3.46).

The rate of AHC infants with a cystic periventricular leucomalacia amounted to 2.8% in 2000, 4.5% in 2004, and on average 3.5% - no significant different rates over the years (p_C=0.17). The frequency tended to increase (p_C=0.26) for LHC infants from 1.8% in 2000 to 6.5% in 2004 with an average rate of 3.5%. None of the SHC children had a cystic PVL in the examined years. The differences between LHC and the AHC children weren't significantly in any year and overall (p_C=0.66 in 2000, p_C=0.59 in 2004, p_C=1.00 overall; LHC versus AHC OR=0.98, 95% CI 0.30-3.28). The relative risk of the AHC

infants to have a cystic PVL amounted to more than twice relative to the rest of the children (p_C=0.20, OR=2.17, 95% CI 0.66-7.15).

3.4% of the surviving infants had a cystic PVL in 1996, 2.2% in 2000, 4.0% in 2004, and on average 3.2%. No significant different frequencies were found over the years (p_C=0.23). None of the children who died in a perinatal centre had a cystic PVL in 1996 and the incidence tended to increase (p_C=0.20, p_L=0.08) to 3.2% in 2000 and 5.3% in 2004. The average rate was 2.5%.

4.4.12.2 Mortality rate

The mortality rate of the infants with no periventricular leucomalacia was on average 12.0%, the one of the infants with an echogenic PVL amounted to 11.1% and the one of the infants with a cystic PVL was 9.4%.
The mortality rate of the infants with no or an echogenic periventricular leucomalacia varied significantly (p_C<0.001) between 12.8% in 1996, 14.7% in 2000 and 7.4% in 2004 with an average mortality rate of 11.9%. None of the infants with a cystic PVL died in 1996 and the mortality rate amounted to 20.0% in 2000, 9.5% in 2004, and on average 9.4% (95% CI 1.3-17.6%). These rates didn't differ significantly over the years (p_C=0.15). The children with a cystic PVL didn't die less frequently than the other infants (p_C=0.58, OR=0.77, 95% CI 0.30-1.96). The mortality rate of the children with an echogenic PVL amounted to 21.7% in 1996, 17.9% in 2000 and 4.5% in 2004; a significant decrease (p_C=0.033).

4.4.13 Neonatal outcome

4.4.13.1 Description

The incidence of good neonatal outcome was 70.7% in 1996, 71.6% in 2000, 70.6% in 2004, and on average 71.0%, no significant yearly changes between the years (p_C=0.71 between 1996 and 2000, p_C=0.69 between 2000 and 2004, p_C=1.00 between 1996 and 2004). 16.9% of the survivors had a poor neonatal outcome in 1996, 13.6% in 2000, 17.9% in 2004, and on average 16.1%. A significant yearly difference was found only between 2000 and 2004 (p_C=0.11 between 1996 and 2000, p_C=0.04 between 2000 and 2004, p_C=0.65 between 1996 and 2004).

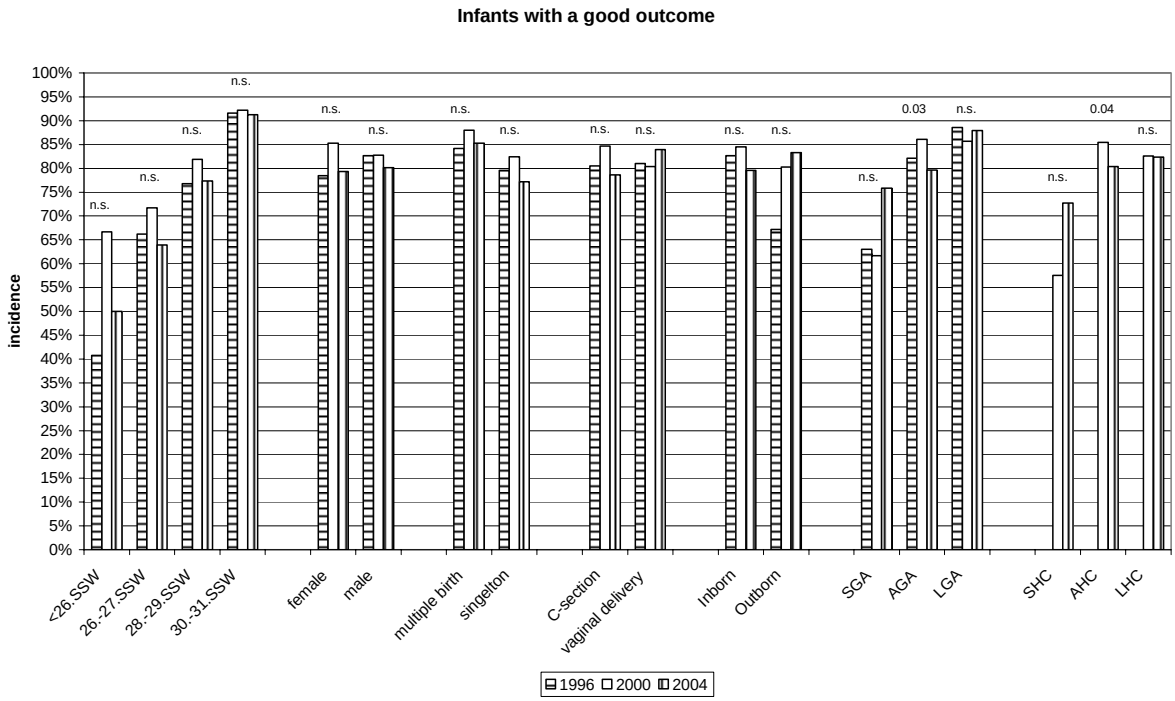
4.4.13.2 A good neonatal outcome

By regarding only the survivors, the incidence of a good outcome amounted to 80.7% in 1996, 84.0% in 2000 and 79.7% in 2004. The rates didn't vary significantly over the years (p_C=0.16). The average rate of infants with a good outcome was 81.5% (95% CI 79.6-83.4%). The minimal frequency in a perinatal centre ranged between 63.9% in 1996, 54.5% in 2000 and 57.4% in 2004 with an average rate of 65.6%. The maximal one was 82.0% in 1996 and 2000, 84.0% in 2004, and on average 79.6%.

The incidence of a good outcome of all infants in the examined years increased significantly with the gestational age (Figure 28): 53.1% of all infants with <26 completed weeks had a good outcome, 67.4% of the ones with 26 and 27 weeks, 78.7% of the ones with 28 and 29 weeks, 91.7% of the ones with 30 and 31 weeks (p=0.011 between infants with <26 weeks and the ones with 26-27 weeks, p<0.001 between all other pair of age groups).
For the infants with <26 weeks, only the difference of the incidence between 1996 and 2000 was significantly (p_C=0.045): the rate was 40.7% in 1996, 66.7% in 2000 and 55.0% in 2004. The rates didn't differ significantly over the years (p_C=0.12). The frequencies of a good outcome tended to remain stable over the years for all other age groups. 66.2% of the infants with 26 and 27 weeks had a good outcome in 1996, 71.7% in 2000 and 63.9% in 2004 (p_C=0.49). The incidence of children with 28 and 29 weeks amounted to 76.8% in 1996, 81.9% in 2000 and 77.4% in 2004 (p_C=0.48). A narrow rate

range was observed for the infants with 30 and 31 weeks: 91.6% in 1996, 92.2% in 2000 and 91.3% in 2004 (p_C=0.92).

Figure 28: Distribution of survivors with a good neonatal outcome per different categories and per year.



The incidence of females with a good outcome didn't differ significantly over the years (p_C=0.09), although the yearly change between 1996 and 2000 was significantly (p_C=0.046): 78.5% in 1996, 85.3% in 2000, 79.3% in 2004, and on average 81.2%. 82.6% of the males had a good outcome in 1996, 82.7% in 2000 and 80.1% in 2004 with an average rate of 81.8%. The differences between the years weren't significantly (p_C=0.66). The rates didn't differ significantly between the gender in any year and overall (p_C=0.24 in 1996, p_C=0.42 in 2000, p_C=0.82 in 2004, p_C=0.74 overall). The relative risk of females to have a poor outcome relative to the males was 1.04 (95% CI 0.81-1.34).

The rates of good outcome tended to remain stable for single and multiple births (singletons p_C=0.19, multiple births p_C=0.63). 84.2% of the multiple births had a good outcome in 1996, 88.0% in 2000 and 85.3% in 2004. The frequencies for the singletons were 79.6% in 1996, 82.4% in 2000 and 77.2% in 2004. The average rates amounted to 85.9% for the multiple and 79.7% for the single births. The two groups had any significant different rates in 2004 and overall (p_C=0.27 in 1996, p_C=0.11 in 2000, p_C=0.027 in 2004, p_C=0.004 overall). The multiple births had a significantly lower overall risk of a poor outcome than the single ones (OR=0.64, 95% CI 0.48-0.87).

The incidences of a good outcome didn't differ significantly between infants born by C-section and vaginal births in any year and on average (p_C=0.90 in 1996, p_C=0.25 in 2000, p_C=0.18 in 2004, p_C=0.82 overall; C-section versus vaginal births OR=1.03, 95% CI 0.77-1.39). The rates for the first differed significantly between 2000 and 2004 (p_C=0.022), however they didn't vary significantly over the years (p_C=0.07): 80.5% in 1996, 84.7% in 2000, 78.6% in 2004, and on average 81.3%. 81.0% of the vaginal born children had a good outcome in 1996, 80.3% in 2000 and 84.0% in 2004 and the average rate was 81.8%. The rates didn't differ significantly over the years (p_C=0.72).

A similar result as for the mode of delivery was obtained for the temporal development of inborns and outborns. 82.6% of the inborns had a good outcome in 1996, 84.5% in 2000, 79.5% in 2004, and on

average 82.1%. A significant result was obtained between 2000 and 2004 (p_C=0.043) with no significant difference over the years (p_C=0.12). The frequency for the outborns tended to remain stable (p_C=0.12) between 67.2% in 1996, 80.3% in 2000 and 83.3% in 2004 with an average rate of 75.6%. The rates of the two groups differed significantly in 1996 and overall (p_C=0.004 in 1996, p_C=0.39 in 2000, p_C=0.61 in 2004, p_C=0.044 overall). The overall odds ratio of the inborns relative to the outborns amounted to 0.68 (95% CI 0.46-0.99).

The SGA infants had a significant lower incidence of a good outcome than AGA and LGA children in 1996, 2000 and overall (between SGA and AGA p=0.002 in 1996, p_C <0.001 in 2000 and overall, p_C=0.49 in 2004; between SGA and LGA p_C=0.009 in 1996, p_C=0.017 in 2000, p_C=0.17 in 2004, p_C <0.001 overall). The relative risk of the SGA children to have a poor outcome was higher than two relative to the AGA ones (OR=2.29, 95% CI 1.58-3.31) and almost seven relative to the LGA ones (OR=7.06, 95% CI 3.51-14.22). No significant difference was observed between AGA and LGA children (p_C=0.33 in 1996, p_C=0.96 in 2000, p_C=0.26 in 2004, p_C=0.22 overall; LGA versus AGA OR=0.65, 95% CI 0.38-1.25). The odds ratio of the AGA infants amounted to 0.65, significantly lower than one relative to the rest of the children (95% CI 0.47-0.89).

The frequency of the SGA infants with a good outcome tended to increase (p_C=0.22) from 63.0% in 1996 respectively 61.7% in 2000 to 75.9% in 2004 with an average rate of 67.5%. The AGA children had a significant higher rate in 2000 than in 2004 (p_C=0.009) and the incidence varied significantly over the years (p_C=0.032): 82.1% in 1996, 86.1% in 2000, 79.7% in 2004, and on average 82.7%. The incidence of LGA infants tended to remain stable (p_C=0.93) between 88.6% in 1996, 85.7% in 2000, 87.9% in 2004 with an average rate of 87.4%.

The SHC infants had as well a significant lower rate than the AHC infants in 2000 and overall (p_C<0.001 in 2000 and overall, p_C=0.22 in 2004; OR=2.46, 95% CI 1.49-4.07). The AGA and LGA didn't differ significantly in the frequencies (p_C=0.60 in 2000, p_C=0.79 in 2004, p_C=0.92 overall; LGA versus AGA OR=1.02, 95% CI 0.56-1.87).
The increase of the SHC children with a good outcome from 57.6% in 2000 to 72.7% in 2004 wasn't significantly (p_C=0.16). The average rate amounted to 66.2%. The AHC infants decreased significantly from 85.4% in 2000 to 80.4% in 2004 (p_C=0.041) with an average rate of 82.8%. The rate of the LHC children remained stable in a narrow range between 82.6% in 2000 and 82.4% in 2004 (p_C=0.96).

69.9% of the infants who had a 1-minute APGAR score below 4 had a good outcome in 2000, 65.8% in 2004 (p_C=0.56). The incidence of a good outcome amounted to 83.7% for the children with a score 4-6 in 2000 and 78.1% in 2004 (p_C=0.17). For the high score group, 89.5% of the infants had a good outcome in 2000 and 84.5% in 2004 (p_C=0.09). The average frequency of a good outcome was 68.1% for the lowest APGAR score group, 80.1% for the middle one and 86.9% for the highest one. Infants with a score below 4 had an almost 2 times higher risk of a poor outcome than the ones of the middle score group (p_C=0.001; OR=1.96, 95% CI 1.31-2.94) and the odds ratio of the latter was 1.59 times compared to children with a score above 6 (p_C=0.011; OR=1.59, 95% CI 1.11-2.27).
For the APGAR score after 5 minutes, 75.0% of the infants with a score below 4 had a good outcome in 2000 and 66.7% in 2004 (p_C=0.71). The frequency amounted to 68.8% for the children with a score 4-6 in 2000 and 66.1% in 2004 (p_C=0.74). 86.7% of the highest score group reached a good outcome in 2000 and 81.6% in 2004, a significant decrease (p_C=0.032). The average incidence of a good outcome amounted to 72.2% for the lowest score group, 67.7% for the middle one and 84.1% for the highest one. Infants with a score below 4 had no significant higher risk of a poor outcome than the ones of the middle score group (p_C=0.71; OR=0.80, 95% CI 0.27-2.39), however the children with a score 4-6 had a 2.53 times higher risk compared to children with a score above 6 (p_C<0.0001; 95% CI 1.70-3.76).
The incidence of a good outcome was 60.0% for the infants with a 10-minutes APGAR score below 4 in 2000. None of the infants had a score below 4 in 2004. 57.7% of the children of the middle score

group had a good outcome in 2000 and 66.7% in 2004 (p_C=0.50). The frequency of a good outcome amounted to 85.5% for the infants with a score above 6 in 2000 and 80.4% in 2004, a significant decrease (p_C=0.029). The average incidence was 60.0% for the lowest score group, 62.3% for the middle one and 82.9% for the highest one. Again the infants with a score below 4 had no significant higher risk of a poor outcome (p_C=0.92; OR=1.10, 95% CI 0.17-7.16) and the odds ratio of the latter amounted to 2.94 (p_C<0.001; 95% CI 1.65-5.24).

4.4.14 Length of stay of the survivors

In this chapter, only the 1458 survivors who were delivered to a perinatal centre and had a known length of stay (LOS) were contemplated: 485 infants in 1996, 509 in 2000 and 464 in 2004. The mean length of stay (Figure 29) tended to decrease from 67.3 days (95% CI 64.6-70.1 days) in 1996 to 65.2 days (95% CI 62.3-68.1 days) in 2000 and 65.0 days (95% CI 62.4-67.6 days) in 2004 (p_C=0.48). The average mean duration of survivors staying in a perinatal centre amounted to 65.8 days (95% CI 64.2-67.4 days).
The decreasing trend of the mean LOS is misleading the trend of LOS because firstly, comparing the curves of 2000 and 2004, there were more children in 2004 than in 2000 staying between 26 and 28 days respectively between 91 and 150 days. There were also more children in 2000 than in 1996 and 2004 staying more than 184 days.

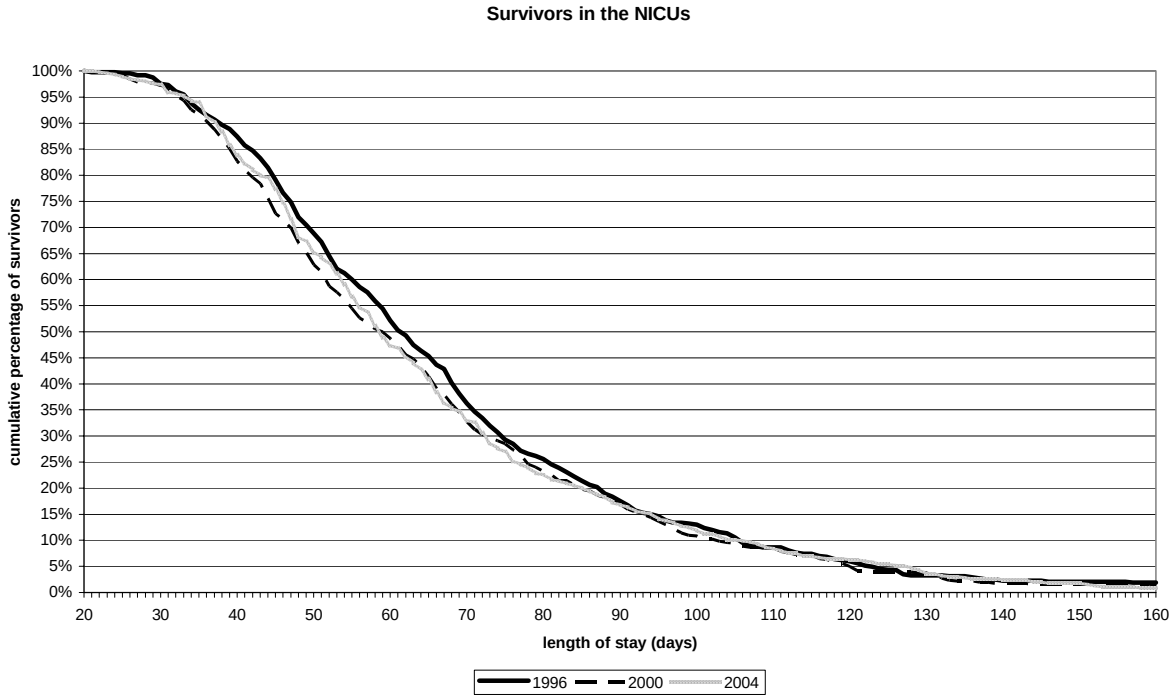
Secondly, the minimal mean LOS in a perinatal centre was 54.2 days in 1996, 59.5 days in 2000 and 56.9 days in 2004 with an average minimal duration of 57.2 days. The maximal mean LOS amounted to 78.9 days in 1996, 76.8 days in 2000, 77.9 days in 2004, and on average 71.2 days.

The gestational age was inversely related with the hospital stay. The infants with <26 completed gestational weeks stayed 102.7 days in 1996, 119.0 days in 2000 and 116.4 days in 2004 – no significant change over the period (p_C=0.39) – and on average 113.3 days (95% CI 104.9-121.4 days). The length of stay of the children with 26-27 completed weeks tended to decrease (p_C=0.18, p_L=0.010) from 100.6 days in 1996 to 88.2 days in 2000 respectively 87.9 days in 2004 with an average LOS of 91.6 days (95% CI 87.9-95.3 days). For the infants with 28-29 completed weeks, the duration of the hospitalisation changed significantly between 74.2 days in 1996, 66.6 days in 2000 and 68.2 days in 2004 (p_C=0.036, p_L=0.038) and amounted on average to 69.7 days (95% CI 67.3-72.1). The children with 30-31 completed weeks were 49.5 days in the hospital in 1996, 48.9 days in 2000 and 46.9 days in 2004 – a significant change between 1996 and 2004 (p_C=0.004) - with an average LOS of 48.5 days (95% CI 47.2-49.8 days).

The females stayed 66.6 days in the hospital in 1996, 64.1 days in 2000 and 65.7 days in 2004 – no significant change (p_C=0.14). The length of stay tended to decrease for the males from 67.9 days in 1996 to 66.2 days in 2000 and 64.3 days in 2004 (p_C=0.20, p_L=0.21). The duration of the hospitalisation amounted to 65.4 days for the females (95% CI 63.2-67.7 days) and 66.2 days for the males (95% CI 63.9-68.5 days). The average LOS didn't differ significantly (p_C=0.40).
The multiple births stayed significantly shorter in the hospital than the singleton (p_C=0.019). For the first, the length of stay was 60.6 days in 1996, 63.4 days in 2000, 62.4 days in 2004 – a significant change (p_C=0.003) – and on average 62.3 days (95% CI 59.7-64.8 days). The latter stayed 69.4 days in the hospital in 1996, 65.9 days in 2000, 66.2 days in 2004 – no significant change over the period (p_C=0.89) – with an average LOS of 67.2 days (95% CI 65.3-69.2 days).
The length of stay tended to decrease (p_C=0.57) for the infants delivered by C-section from 67.9 days in 1996 to 66.1 days in 2000 and 65.5 days in 2004. The vaginal delivered children stayed 65.6 days in the hospital in 1996, 62.9 days in 2000 and 63.4 days in 2004 – no significant change (p_C=0.18). The average LOS amounted to 66.5 days (95% CI 64.7-68.3 days) for the infants with C-section and was

significantly longer (p_C=0.035) than the 64.0 days (95% CI 60.5-67.5 days) of the vaginal delivered ones.

Figure 29: Temporal development of the remaining survivors per year.



The inborns had a hospital stay of 67.0 days in 1996, 64.6 days in 2000, 65.2 days in 2004, and on average 65.5 days (95% CI 63.9-67.2 days). For the outborns, the LOS amounted to 69.6 days in 1996, 70.5 days in 2000, 60.9 days in 2004 with an average amount of 68.7 days (95% CI 63.9-73.6 days). For both groups, the duration didn't change significantly over the years (inborn p_C=0.62, outborn p_C=0.12). The LOS didn't differ significantly between the inborns and outborns either (p_C=0.13).
The birth weight was associated with the length of stay as well. For the small for gestational age infants, the length of stay tended to decrease (p_C=0.18) from 86.1 days in 1996 to 81.7 days in 2000 and 70.3 days in 2004. The AGA children were 66.1 days in the hospital in 1996, 64.0 days in 2000 and 64.6 days in 2004 (p_C=0.15). The LGA ones had a duration of 54.6 days in 1996, 56.5 days in 2000 and 59.4 days in 2004 (p_C=0.53). The average LOS was 79.0 days for the SGA infants (95% CI 73.8-84.2 days) and significantly higher (p_C<0.0001) than the 64.9 days for the AGA ones (95% CI 63.2-66.6 days). The LGA children stayed on average 56.6 days (95% CI 51.7-61.5 days), not significantly shorter than the AGA ones (p_C=0.25).

The maximal age at dismission was $63^1/_7$ weeks' PMA (LOS 255 days, birth weight 990g, major congenital malformation – lung hypoplasy after oligohydramnion) in 1996, 79 weeks' PMA (LOS 372 days, birth weight 880g, major congenital malformation – uncertain syndrome) in 2000 and $56^6/_7$ weeks' PMA (LOS 213 days, birth weight 660g, short bowel syndrome) in 2004. The mean age at dismission amounted to $39^1/_7$ weeks' PMA in 1996, $38^5/_7$ in 2000, $38^4/_7$ in 2004, and on average $38^6/_7$ weeks. The age at dismission didn't vary significantly over the years (p_C=0.21). The survivors with an age at dismission above 50 weeks' PMA stayed maximal 372 days in the hospital. The infants who were released to home at an age of 50-55 completed weeks' PMA had significantly more frequently a proven NEC, a CLD and/or a BPD than all survivors (Table 14). The children with 55-60 completed weeks' PMA at dismission had only a higher risk of a proven NEC and the ones with more than 60 completed weeks had significantly more often a major congenital malformation, a proven sepsis and/or

a BPD. For all three age groups at dismission, the infants had a significantly higher risk of a poor outcome relative to all survivors.

Table 14: Statistics of infants with an age at dismission >50 completed weeks' PMA.

GA at dismission (completed weeks)	$50^1/_7$-55	$55^1/_7$-60	> 60
n	8	5	6
min LOS	140	185	223
min BW	570	660	640
min pH-value of umbilical artery	7.13	7.24	7.03
min APGAR after 5 min	7	8	4
Female	62.5%	80.0%	33.3%
Multiple birth	0.0%	20.0%	16.7%
C-section	75.0%	100.0%	83.3%
SGA	25.0%	0.0%	16.7%
SHC	33.3%	33.3%	0.0%
Major congenital malformation	12.5%	0.0%	50.0%[c]
Proven sepsis	25.0%	100.0%	50.0%[b]
Proven NEC	25.0%[c]	20.0%[b]	0.0%
Respiratory distress	100.0%	80.0%	100.0%
CLD	75.0%[b]	60.0%	66.7%
BPD	75.0%[c]	40.0%	50.0%[b]
Intracranial haemorrhage grade 3-4	0.0%	20.0%	16.7%
Poor neonatal outcome	75.0%[c]	60.0%[a]	66.7%[b]

Significant difference from all survivors:
a: $p_C<0.05$
b: $p_C<0.01$
c: $p_C<0.0001$

4.5 Therapy of the liveborns in the perinatal centres

4.5.1 Antenatal steroids

4.5.1.1 Description

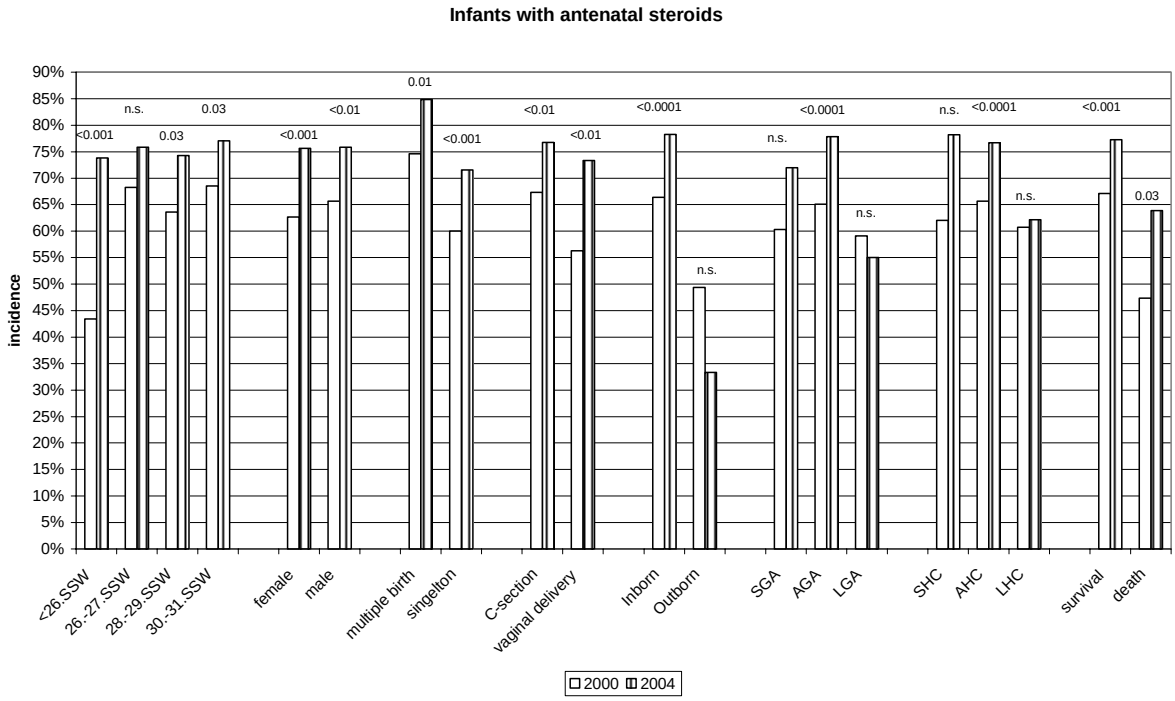
The amount of infants with antenatal steroids in the perinatal centres rose significantly from 64.2% in 2000 to 75.7% in 2004 ($p_C<0.0001$). The average rate amounted to 69.9% (95% CI 67.4-72.4%). The minimal rate of infants in one of the perinatal centres was 52.4% in 2000, 40.4% in 2004, and on average 57.1%. The maximal rate was 81.8% in 2000, 92.0% in 2000, and on average 84.5%.

The amount of infants with antenatal steroids can be separated into two groups: those children who received a surfactant therapy as well and those without a surfactant therapy. The frequency of the latter group stayed at the same level 49.9% of all infants in 2000 - 74.6% of the infants with antenatal steroids - and 2004 - 63.3% of the infants with antenatal steroids. The first group increased from 16.3% in 2000 to 27.8% of all infants in 2004 respectively 25.4% of all infants with antenatal steroids in 2000 and 36.7% in 2004.

A significant increase in the frequency of infants with antenatal steroids rose significantly for all age groups except the infants with 26-27 completed weeks (Figure 30). 43.4% of the infants with <26 weeks had antenatal steroids in 2000, 73.8% in 2004 ($p_C <0.001$), and on average 57.4%. The rate for the children with 26-27 weeks amounted to 68.2% in 2000, 75.8% in 2004 ($p_C=0.18$), and on average 71.9%. The frequency of infants with antenatal steroids and 28-29 weeks rose from 63.6% in 2000 to 74.3% in 2004 ($p_C=0.032$) with an average rate of 68.9%. The significant rate for the oldest age group was from 68.5% in 2000 to 77.0% in 2004 ($p_C=0.027$) and amounted on average to 72.8%.

Overall, the youngest children had a significant lower frequency of antenatal steroids than the other age groups (infants with 26-27 weeks p_C=0.003, infants with 28-29 weeks p_C=0.016, infants with 30-31 weeks p_C <0.001). The rate of given antenatal steroids didn't differ significantly between the other pairs of age groups (between infants with 26-27 weeks and infants with 28-29 weeks p_C=0.43, between infants with 26-27 weeks and infants with 30-31 weeks p_C=0.80, between infants with 28-29 weeks and infants with 30-31 weeks p_C=0.21).

Figure 30: Distribution of infants with antenatal steroids per different categories and per year.



The rate of the females with antenatal steroids rose significantly from 62.7% in 2000 to 75.6% in 2004 with an average rate of 68.9% (p_C <0.001). The increase for the males was significantly as well (p_C=0.004): 65.7% in 2000, 75.8% in 2004, and on average 70.8%. The gender didn't show any significant different rates in any year and overall (p_C=0.43 in 2000, p_C=0.94 in 2004, p_C=0.46 overall; female versus male OR=0.91, 95% CI 0.72-1.16).

The frequency of given antenatal steroids differed significantly between single and multiple births in 2000, 2004 and overall (p_C <0.001). The latter had an almost doubled overall risk to receive antenatal steroids (OR=2.09, 95% CI 1.57-2.77) relative to the singletons. A significant increase of given antenatal steroids was seen for singletons (p_C <0.001): 74.6% in 2000, 84.8% in 2004, and on average 79.9%. The multiple births got significantly more antenatal steroids in 2004 than in 2000 (p_C=0.012): 60.0% in 2000, 71.5% in 2004, and on average 65.6%.

67.3% of the infants born by C-section received antenatal steroids in 2000 and this rate increased significantly to 76.8% in 2004 (p_C=0.001); the average rate for this group was 72.0%, for the vaginal births amounted to 64.8%. The frequency of the latter increased significantly from 56.3% in 2000 to 73.3% in 2004 as well (p_C=0.002). The two groups differed significantly in 2000 and on average (p_C=0.014 in 2000, p_C=0.39 in 2004, p_C=0.016 overall).

Inborns got significantly more antenatal steroids in 2004 than in 2000 (p_C <0.0001): 66.4% in 2000, 78.3% in 2004, and on average 72.5%. The rates of outborns with antenatal steroids tended to remain stable (p_C=0.11) and varied between 49.3% in 2000 and 33.3% in 2004 with an average rate of 44.1%.

Antenatal steroids were given significantly more to inborns than to outborns (p_C=0.004 in 2000, p_C <0.0001 in 2004 and overall). The odds ratio of the inborns to receive antenatal steroids amounted to 3.33 relative to the outborns (95% CI 2.24-4.95).

The rate of SGA infants with antenatal steroids tended to rise (p_C=0.14) from 60.3% in 2000 to 72.0% in 2004. The rise from 65.1% in 2000 to 77.9% in 2004 was significantly (p_C<0.001) for the AGA children. 59.1% of the LGA infants had antenatal steroids in 2000 and 55.0% in 2004, no significant decrease (p_C=0.71). The average rate amounted to 66.4% for the SGA, 71.4% for the AGA and 57.1% for the LGA infants. SGA and AGA children didn't have significant different frequencies (p_C=0.44 in 2000, p_C=0.26 in 2004, p_C=0.22 overall; SGA versus AGA OR=0.79, 95% CI 0.55-1.15). AGA children received significantly more antenatal steroids than LGA ones in 2000 and on average (p_C=0.43 in 2000, p_C=0.010 in 2004, p_C=0.006 overall; LGA versus AGA OR=0.53, 95% CI 0.34-0.84). The relative risk of AGA children to receive antenatal steroids was significantly higher than one relative to the rest of the infants (p_C=0.013, OR=1.46, 95% CI 1.98).

The increase for SHC and LHC infants wasn't significantly (SHC p_C=0.07, LHC p_C=0.89). 62.0% of the SHC infants got antenatal steroids in 2000, 78.2% in 2004 and 70.5% on average. The rate for LHC children tended to remain stable: 60.7% in 2000, 62.2% in 2004, and on average 61.3%. A significant increase of antenatal steroids showed the AHC children (p_C <0.0001). SHC and AHC children didn't have any significantly different rate of antenatal steroids (p_C=0.60 in 2000, p_C=0.81 in 2004, p_C=0.86 overall; SHC versus AHC OR=0.96, 95% CI 0.62-1.49). The rate of antenatal steroids was significantly higher for the AHC than for the LHC infants in 2004 and on average (p_C=0.46 in 2000, p_C=0.047 in 2004, p_C=0.044 overall; LHC versus AHC OR=0.64, 95% CI 0.41-0.99). The AHC children didn't have a significant different frequency of steroid application than the rest of the infants (p_C=0.97; OR=1.00, 95% CI 0.83-1.21).

67.1% of the survivors got antenatal steroids in 2000 and this rate increased significantly to 77.2% in 2004 (p_C <0.001) with an average rate of 72.2%. The increase from 47.4% in 2000 to 63.9% in 2004 was significantly for the infants who died in the perinatal centres (p_C=0.034).

4.5.1.2 Mortality rate

The mortality rate of the infants with antenatal steroids tended to remain stable (p_C=0.55): 10.9% in 2000, 9.6% in 2004 with an average rate of 10.2% (95% CI 8.2-12.2%). 21.6% of the infants who didn't received any antenatal steroids died in 2000, 17.0% in 2004; no significant difference p_C=0.26). The average rate was 19.8% (95% CI 15.8-23.8%). The mortality rates differed significantly between the two groups (p_C <0.001 in 2000 and overall, p_C=0.013 in 2004). The relative risk of the infants with antenatal steroids to die relative to the ones without any antenatal steroids amounted to 0.47 (95% CI 0.33-0.64).
The mortality rate for the infants who received antenatal steroids and surfactant amounted to 22.9% in 2000, 20.6% in 2004, and on average 21.4%. 6.8% of the infants who received antenatal steroids only and no surfactant died in 2000, 3.3% in 2004 and 5.1% on average.

4.5.2 Surfactant

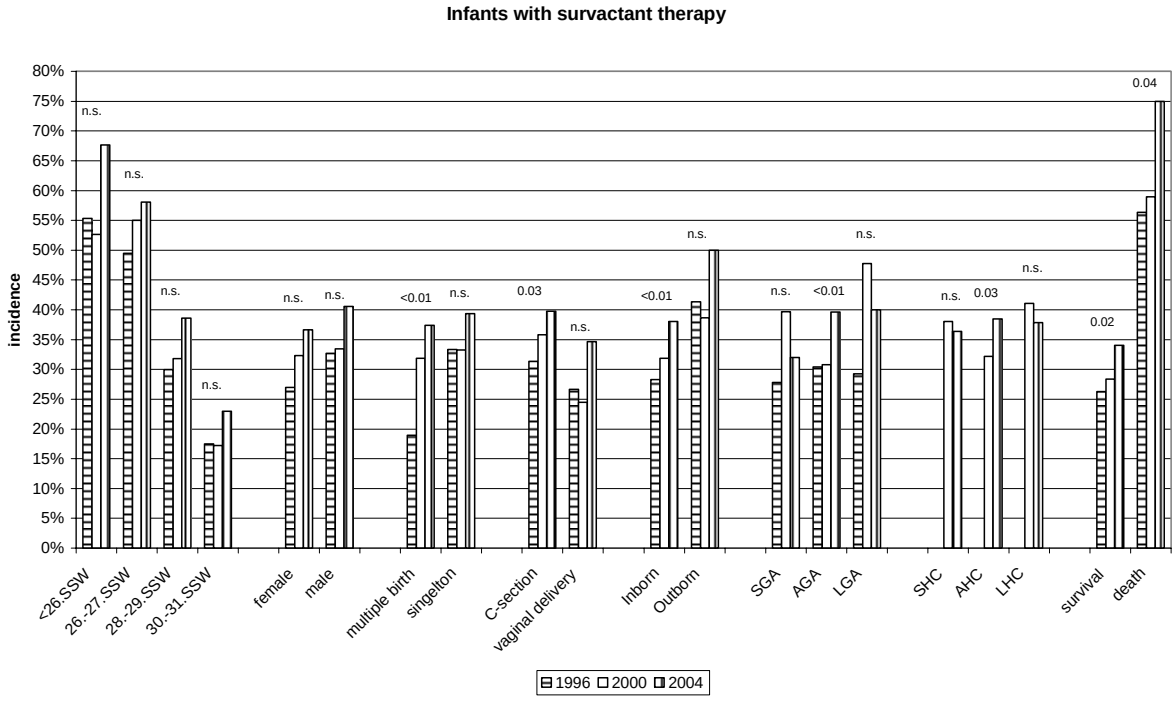
4.5.2.1 Description

The frequency of infants who got a surfactant therapy amounted to 30.0% in 1996, 32.9% in 2000, 38.7% in 2004, and on average 34.0% (95% CI 31.8-36.1%). The rates differed significantly over the years (p_C=0.005). The minimal rate within perinatal centres was 17.1% in 1996, 16.7% in 2000, 25.0% in 2004, and on average 20.1%. The maximal rate amounted to 64.3% in 1996, 63.6% in 2000, and 66.2% in 2004 with an average rate of 63.9%.

16.6% of all children only received a surfactant therapy but no antenatal steroids in 2000 and 11.0% in 2004. Overall only 13.8% of the children got only a surfactant factor (95% CI 11.9-15.7%). The frequency of infants with surfactant and antenatal steroids amounted to 16.3% of all infants in 2000 and 27.8% in 2004. 49.5% of the infants with a surfactant therapy received antenatal steroids in 2000 and 71.7% in 2004, too.

The frequency of infants with <26 completed weeks and surfactant therapy (Figure 31) amounted to 55.4% in 1996, 52.6% in 2000 and 67.7% in 2004, no significant increase (p_C=0.17). An increasing trend (p_C=0.45) could be observed for the infants with 26-27 weeks: 49.5% in 1996, 55.0% in 2000 and 58.1% in 2004. A similar trend (p_C=0.20, p_L=0.09) was seen for infants with 28-29 weeks: 29.9% in 1996, 31.8% in 2000 and 38.6% in 2004. 17.5% of the infants with 30-31 weeks received a surfactant therapy in 1996, 17.2% in 2000 and 23.0% in 2004; no significant changes over the years (p_C=0.17).
The average rate was 58.4% for the infants with <26 weeks, 54.6% for the ones with 26-27 weeks, 33.5% for the ones with 28-29 weeks and 19.3% for the ones with 30-31 weeks. The difference between the youngest two age groups were the only not significant ones (p_C=0.40). All other pairs of age groups were highly significantly (p_C<0.0001) i.e. the rate of surfactant therapy decreased significantly with the gestational age.
The frequency of a single surfactant application without any antenatal steroids decreased with the gestational age: 27.0% of the children with <26 weeks, 19.0% of the ones with 26-27 weeks, 13.1% of the ones with 28-29 weeks and 8.4% of the ones with 30-31 weeks.

Figure 31: Distribution of infants with surfactant per different categories and per year.



The increase between 1996 and 2004 wasn't significantly for the females over the years (p_C=0.05, p_L=0.015) however between 1996 and 2004 (p_C=0.015): 27.0% in 1996, 32.3% in 2000, 36.6% in 2004, and on average 32.1%. The same holds for the males (p_C=0.07, p_L=0.034) with a significant yearly change between 1996 and 20004 (p_C=0.037): 32.7% in 1996, 33.4% in 2000, 40.6% in 2004, and on average 35.7%. The gender didn't have significantly different rates of surfactant therapy (p_C=0.14 in 1996, p_C=0.75 in 2000, p_C=0.30 in 2004, p_C=0.11 overall; female vs. male OR=0.85, 95% CI 0.70-1.04).

Overall, 12.4% of the females and 15.1% of the males only received surfactants and no antenatal steroids (female versus male p_C=0.18, OR=0.80, 95% CI 0.58-1.10).

18.9% of the multiple births got a surfactant therapy in 1996, 31.9% in 2000 and 37.4% in 2004; a significant difference over the years (p_C=0.002, p_L<0.001). The singletons with surfactant remained stable (p_C=0.10, p_L=0.06) and varied between 33.3% in 1996 and 2000 respectively 39.4% in 2004. The average rate was 30.7% for the multiple and 35.3% for the single births. The two groups differed significantly only in 1996 (p_C=0.002 in 1996, p_C=0.74 in 2000, p_C=0.63 in 2004, p_C=0.06 overall; multiple versus single births OR=0.81, 95% CI 0.65-1.01).
Only surfactant was given to 10.4% of the multiple births and 15.2% of the singletons. The first received significantly less than the latter (p_C=0.022, OR=0.65, 95% CI 0.45-10.94).

The difference between 1996 and 2004 was significantly for the infants born by C-section (p_C=0.034, p_L=0.010): 31.4% in 1996, 35.8% in 2000, 39.7% in 2004, and on average 35.9%. The vaginal delivered infants had a stable frequency of surfactant therapy (p_C=0.12): 26.7% in 1996, 24.5% in 2000, 34.7% in 2004, and on average 28.5%. A significant difference was found for the mode of delivery in 2000 and on average (p_C=0.27 in 1996, p_C=0.010 in 2000, p_C=0.26 in 2004, p_C=0.004 overall). The odds ratio of the children born by C-section relative to the vaginal births amounted to 1.40 (95% CI 1.11-1.76).
14.0% of the infants with C-sections and 12.3% of the vaginal births only received surfactant; no significant difference (C-section versus vaginal births p_C=0.44, OR=1.17, 95% CI 0.79-1.72).

28.3% of the inborn had a surfactant therapy and this rate increased to 31.9% in 2000 respectively to 38.0% in 2004. The rates varied significantly over the years (p_C=0.002, p_L<0.001). The frequency of outborn tended to remain stable (p_C=0.52): 41.3% in 1996, 38.7% in 2000 and 50.0% in 2004. Inborns had a significant lower rate than outborn in 1996 and overall (p_C=0.022 in 1996, p_C=0.24 in 2000, p_C=0.15 in 2004, p_C=0.015 overall). The relative risk of the inborns to get a surfactant factor was 0.68 relative to the outborns (95% CI 0.50-0.93).
Overall, only surfactant was given to 11.8% of the inborns and 33.3% of the outborns. The latter had a 3.74 higher relative risk to receive only surfactant than the inborns (p_C <0.001, 95% CI 2.43-5.77).

Stable frequencies were observed for SGA infants (p_C=0.36): 27.8% in 1996, 39.7% in 2000 and 32.0% in 2004. 30.4% of the AGA children received a surfactant therapy in 1996, 30.8% in 2000 and 39.6% in 2004; a significant variation of rates over the years (p_C=0.002, p_L=0.001). The frequency of LGA infants with surfactant amounted to 29.3% in 1996, 47.7% in 2000 and 40.0% in 2004; no significant differences (p_C=0.22).
The average rate was 33.5% for the SGA, 33.6% for the AGA and 39.2% for the LGA infants. The SGA and AGA children didn't have any significant different rates at all (p_C=0.89 in 1996, p_C=0.41 in 2000, p_C=0.39 in 2004, p_C=0.29 overall; SGA versus AGA OR=0.99, 95% CI 0.73-1.36). The rates differed significantly between AGA and LGA infants only in 2000 (p_C=0.89 in 1996, p_C=0.020 in 2000, p_C=0.97 in 2004, p_C=0.21 overall; LGA versus AGA OR=1.27, 95% CI 0.87-1.85).
13.3% of the SGA and the AGA infants and 21.4% of the LGA ones only received surfactant and no antenatal steroids. The odds ratio of the LGA children relative to the AGA ones amounted to 1.78 (p_C=0.039, 95% CI 1.03-3.09).

A stable rate was observed for the SHC infants: 38.0% in 2000 and 36.4% in 2004 (p_C=0.87) with an average rate of 37.1%. The rate of the AHC children with surfactants increased significantly from 32.1% in 2000 to 38.4% in 2004 (p_C=0.034) and amounted on average to 35.4%. The decrease of the LHC infants from 41.1% in 2000 to 37.8% in 2004 wasn't significantly (p_C=0.76). SGA and AGA children had the same risk to get a surfactant therapy (p_C=0.39 in 2000, p_C=0.77 in 2004, p_C=0.72 overall; SHC versus AHC OR=1.08, 95% CI 0.71-1.64). No significant difference can be found

between the LHC and the AHC infants (p_C=0.18 in 2000, p_C=0.94 in 2004, p_C=0.39 overall; LHC versus AHC OR=1.21, 95% CI 0.78-1.86).
Only surfactant was overall given to 14.3% of the SHC infants, 13.3% of the AHC ones and 19.4% of the LHC ones. The risk of SHC infants relative to the AHC ones to receive only surfactant amounted to 1.08 (p_C=0.79, 95% CI 0.61-1.93). The odds ratio of LHC children relative to the AHC ones was 1.56 (p_C=0.11, 95% CI 0.90-2.69).

26.3% of the survivors got a surfactant therapy in 1996 and 28.4% in 2000 and the rates increased significantly (p_C=0.016, p_L=0.005) to 34.1% in 2004. The same result (p_C=0.039, p_L=0.021) was given for the infants who died in a perinatal centre: 56.3% of these infants received surfactant in 1996, 58.9% in 2000 and 75.0% in 2004. On average, 29.7% of the survivors and 63.0% of the dying infants received surfactant.
Overall, 11.4% of the survivors and 29.9% of the infants who died in a perinatal centre only received surfactant.

4.5.2.2 Mortality rate

The mortality rate of the infants who received surfactant was 23.3% in 1996, 26.4% in 2000, 22.1% in 2004, and on average 23.9% (95% CI 20.5-27.2%). These rates didn't differ significantly over the years (p_C=0.55). 7.7% of the infants with no surfactant died in 1996, 9.0% in 2000, 4.7% in 2004, and on average 7.2% (95% CI 5.8-8.7%); a weak significant difference over the years (p_C=0.050). The infants with surfactant died significantly more than those without surfactant (p_C<0.0001 in all years and overall) due to the fact that those infants got the surfactant, because they were more sick. The children with surfactant died about four times more frequently than the others (OR=4.04, 95% CI 3.04-5.36).

By contemplating only the infants who had RDS, 22.2% of the ones died in 1996 who received surfactant, 27.1% in 2000, 21.4% in 2004 – no significant yearly changes (p_C=0.34) - and on average 23.6%. Those who didn't receive surfactant had a mortality rate of 7.4% in 1996, 10.4% in 2000, 4.6% in 2000 – a significant change over the years (p_C=0.019) - and on average 7.4%. The odds ratio for the children with surfactant amounted to 3.83 (95% CI 2.82-5.22; p_C<0.0001).
For the infants with CLD or BPD, no significant mortality rate was found between a treatment with and without surfactant (CLD p_C=0.36, BPD p_C=0.94). For the CLD, 3.9% of the infants with surfactant died in 1996, 6.0% in 2000, 4.1% in 2004 – no significant changes (p_C=0.79) – with an average rate of 4.7% and the mortality rate of the children without treatment amounted to 2.2% in 1996, 4.4% in 2000, 3.0% in 2004 – no significant changes either (p_C=0.73) – and on average 3.1%.
7.9% of the infants with BPD and surfactant died in 1996, 2.5% in 2000 and none in 2004; no significant changes (p_C=0.12).The mortality rate of those without treatment was 5.7% in 1996, 2.6% in 2004 and none died in 2000; no significant changes either (p_C=0.42). The average lethality amounted to 3.3% for the children with surfactant and 3.0% without treatment.
29.9% of the infants who only received surfactant and no antenatal steroids died in 2000, 26.1% in 2004, and on average 28.4% (95% CI 21.7%-35.1%). They had a more than three times higher risk to die than the rest of the infants (p_C <0.001, OR=3.33, 95% CI 2.28-4.87).

4.5.3 Mechanical ventilation

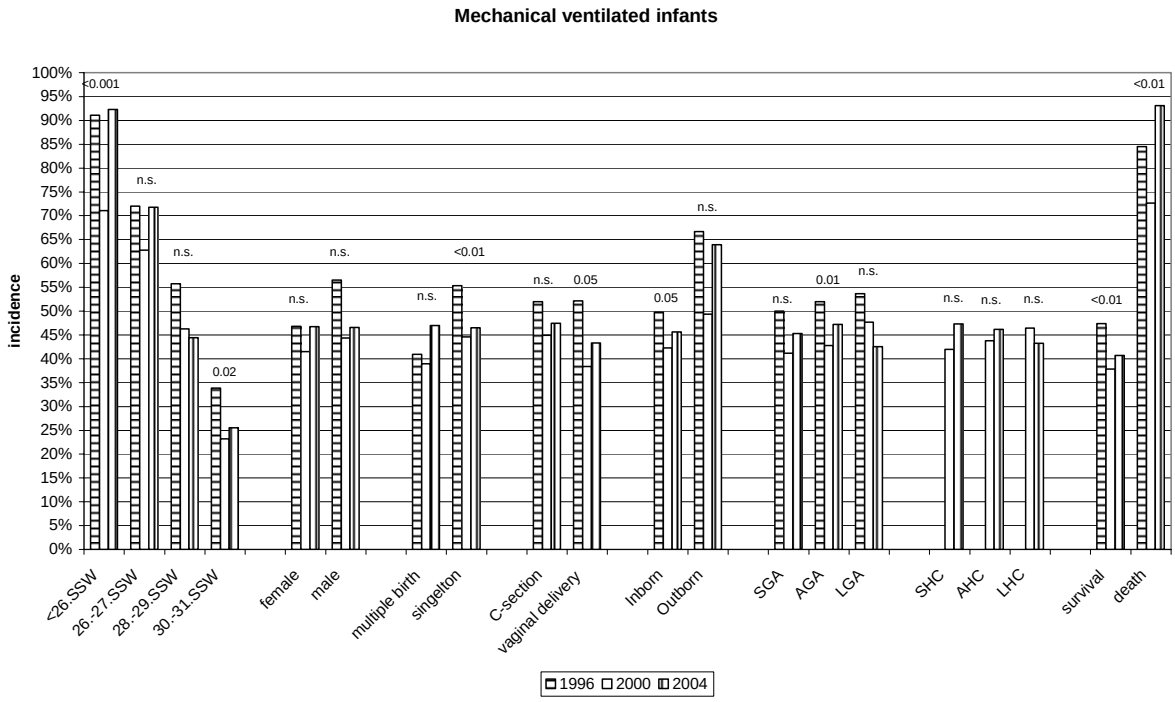
4.5.3.1 Description

The frequency of infants with mechanical ventilation was 52.0% in 1996, 42.9% in 2000 and 46.7% in 2004. The rates varied significantly over the years (p_C=0.007). 47.0% of the infants had mechanical ventilation on average 95% (CI 44.7-49.3%). The minimal rate in a perinatal centre was 30.0% in

1996, 30.4% in 2000, 37.2% in 2004, and on average 40.4%. The maximal rate amounted to 84.1% in 1996, 77.0% in 2000, 67.7% in 2004, and on average 72.1%.

The application of mechanical ventilation decreased significantly with gestational age (p_C<0.001 between any two age groups): 83.8% of the infants with <26 completed weeks were ventilated, 68.5% of the ones with 26-27 weeks, 48.7% of the ones with 28-29 weeks, 27.5% of the ones with 30-31 weeks (Figure 32).
91.1% of the infants with <26 weeks were ventilated in 1996, 71.1% in 2000 and 92.3% in 2004. The differences were significantly (p_C<0.001). The frequency of ventilated infants with 26-27 weeks amounted to 72.0% in 1996, 62.8% in 2000 and 71.8% in 2004; no significant changes (p_C=0.21). The decrease from 55.7% of the infants with 28-29 weeks in 1996 to 44.4% in 2004 was significantly (p_C=0.039), however no significant difference with 44.4% in 2000; the rates didn't vary significantly over the years (p_C=0.09). A significant decrease was seen for the infants with 30-31 weeks (p_C=0.017): 33.9% in 1996, 23.2% in 2000 and 25.6% in 2004.

Figure 32: Distribution of infants with antenatal steroids per different categories and per year.



The frequency of females with ventilation tended to remain stable over the years (p_C=0.31): 46.8% in 1996 and 2004 and 41.5% in 2000. The rate of ventilated males decreased significantly (p_C=0.005) from 56.5% in 1996 to 44.4% in 2000 respectively 46.6% in 2004. The average frequency was 44.9% of the females and 49.0% of the males, no significant difference (p_C=0.08; female versus male OR=0.85, 95% CI 0.71-1.02). The gender differed significantly only in 1996 (p_C=0.020 in 1996, p_C=0.45 in 2000, p_C=0.96 in 2004).

40.9% of the multiple births were ventilated in 1996, 38.9% in 2000, 47.0% in 2004, and on average 42.5%. These rates weren't significantly different (p_C=0.26). A significant decrease was observed for the singletons (p_C=0.003): 55.3% in 1996, 44.6% in 2000, 46.5% in 2004, and on average 48.8%. The rates of ventilated singletons were significantly higher than the ones of ventilated multiple births in 1996 and overall (p_C=0.004 in 1996, p_C=0.19 in 2000, p_C=0.92 in 2004, p_C=0.016 overall; multiple versus single births OR=0.78, 95% CI 0.63-0.95).

The frequency of ventilated infants born by C-section amounted to 52.0% in 1996, 44.9% in 2000, 47.5% in 2004, and on average 47.9%. Only the yearly change between 1996 and 2000 was significantly (p_C=0.036) although the rates didn't vary significantly over the years (p_C=0.11). 52.1% of the vaginal births were mechanical ventilated in 1996, 38.4% in 2000, 43.3% in 2004, and on average 44.8%. The rates varied significantly over the years (p_C=0.045). Obviously the two groups didn't differ significantly in the rates (p=0.97 in 1996, p=0.16 in 2000, p=0.38 in 2004, p=0.25 overall; C-section versus vaginal delivery OR=1.13, 95% CI 0.92-1.40).

49.8% of the inborns were ventilated in 1996, 42.3% in 2000, 45.6% in 2004; a significant difference over the years (p_C=0.048). The frequency of ventilated outborns amounted to 66.7% in 1996, 49.3% in 2000 and 63.9% in 2004; a significant yearly change between 1996 and 2000 (p_C=0.032) without an overall significant difference (p_C=0.08). The average rate was 45.7% of the inborns and 59.1% of the outborns. The outborns were significantly ventilated more frequently than inborns (p_C=0.006 in 1996, p_C=0.24 in 2000, p_C=0.033 in 2004, p_C<0.001 overall; inborn versus outborn OR=0.58, 95% CI 0.43-0.79).

The SGA, AGA and LGA infants didn't differ significantly in the frequency of mechanical ventilation. On average, 45.2% of the SGA infants were ventilated, 47.1% of the AGA ones and 48.0% of the LGA ones (SGA versus AGA p_C=0.61, OR=0.92, 95% CI 0.69-1.24; LGA versus AGA p_C=0.85, OR=1.03, 95% CI 0.72-1.49).
The frequency of ventilated SGA children tended to remain stable (p_C=0.62): 50.0% in 1996, 41.2% in 2000 and 45.3% in 2004. For the AGA infants, the rates varied significantly over the years (p_C=0.014) between 52.0% in 1996, 42.8% in 2000 and 47.2% in 2004. The 53.7% of the LGA children were ventilated in 1996, 47.7% in 2000 and 42.5% in 2004; no significant decrease (p_C=0.60).

No significant increase (p_C=0.59) from 42.0% in 2000 to 47.3% in 2004 was found for the SHC infants. The frequency of ventilated AHC children tended to increase from 43.8% in 2000 to 46.2% in 2004 as well (p_C=0.43). The decrease from 46.4% in 2000 to 43.2% in 2004 wasn't significantly for the LHC infants (p_C=0.77). The three groups didn't have significantly different rates of mechanical ventilation (SHC versus AHC p=0.96, OR=0.99, 95% CI 0.66-1.48; LHC and AHC p=1.0, OR= 1.01, 95% CI 0.66-1.54).

47.4% of the survivors were ventilated in 1996, 37.8% in 2000, 40.7% in 2004, and on average 41.8%; significant differences over the years (p_C=0.006). The frequency of infants who died in a perinatal centre and were ventilated amounted to 84.5% in 1996, 72,6% in 2000, 93.1% in 2004, and on average 82.4% with significant differences over the years as well (p_C=0.02).

4.5.3.2 Mortality rate

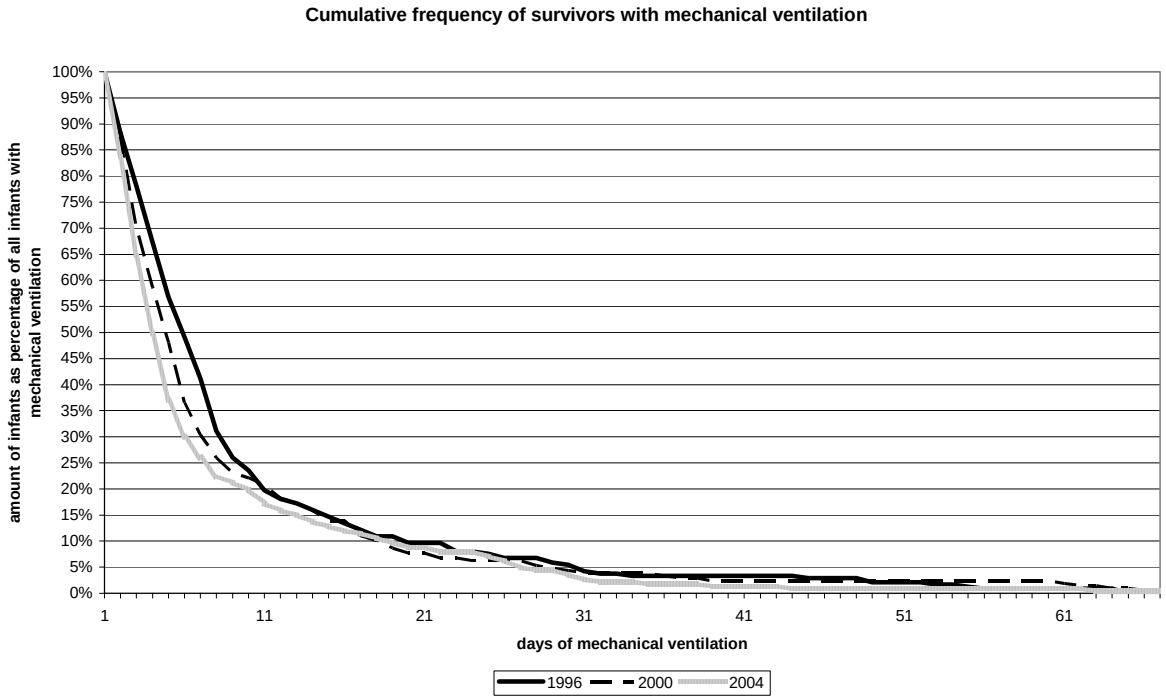
The mortality rate of the ventilated infants was significantly higher than the rate for the infants without any ventilation (p_C<0.001 in all years and overall). 20.1% of the ventilated infants died in 1996, 24.9% in 2000, 22.8% in 2004, and on average 22.6% (95% CI 19.8-25.3%); a significant difference only between 2000 and 2004 (p_C <0.001) although the rates didn't differ significantly over the years (p_C=0.39). The mortality rate for the non-ventilated infants varied significantly over the years (p_C=0.001): 4.0% in 1996, 7.1% in 2000, 1.5% in 2004, and on average 4.3% (95% CI 3.0-5.6%).
For the children with RDS, the mechanical ventilated ones had a significantly higher mortality rate than those without ventilation (p_C<0.0001; OR 6.46, 95% CI 4.35-9.60). 19.3% of the first died in 1996, 25.7% in 2000, 21.9% in 2004 – no significant change over the years (p_C=0.21) – with an average mortality rate of 22.3%. The non-ventilated infants had a mortality rate of 3.2% in 1996, 8.1% in 2000, 1.4% in 2004 - significant differences over the years (p_C<0.001) – and on average 4.2%.
Also for the children with CLD, the difference in the lethality was significantly between the ones with and without mechanical ventilation (p_C=0.010; OR 8.91, 95% CI 1.18-67.14). The first had a mortality

rate of 4.2% in 1996, 6.5% in 2000 and 5.4% in 2004 – no significant yearly changes (p_C=0.74). None of the non-ventilated infants died in 1996 and 2004 and 2.2% in 2004 – no significant yearly changes (p_C=0.28). The average mortality rate amounted to 5.3% for the ventilated and 0.6% for the non-ventilated children.
No significant different mortality rate was observed between the ventilated and the non-ventilated infants who suffered a BPD (p_C=0.10). None of the children without ventilation died between 1996 and 2004. 8.6% of the ventilated infants died in 1996, 2.1% in 2000, 1.8% in 2004 – no significant decrease (p_C=0.13, p_L=0.07) – and on average 4.3%.

4.5.3.3 The duration of mechanical ventilation

The mean duration of mechanical ventilation of the 673 mechanical ventilated survivors amounted to 8.6 days in 1996 and decreased to 7.9 days in 2000 and 6.9 days in 2004 (Figure 33). This decrease wasn't significantly (p_C=0.07, p_L=0.08). The mean duration of these survivors was overall 7.8 days (95% CI 7.0-8.6 days). Almost 90% of the infants were mechanical ventilated shorter than 19 days in all years.
The minimal mean time application of mechanical ventilation in one of the perinatal centres was 4 days in 1996, 4.3 days in 2000 and 3.3 days with an average mean duration of 5.0 days. The maximal mean duration in one of the perinatal centres was 15.4 days in 1996, 16.3 days in 2000 and 14.1 days in 2004, and on average 15.3 days.

Figure 33: Cumulative frequency of infants with mechanical ventilation per year.



For the mechanical ventilated survivors, the duration of the mechanical ventilation as percentage of the length of stay varied between 0.7% and 52%. The survivors with the duration of mechanical ventilation between 30% and 40% of LOS had significantly more frequently a proven NEC, CLD, BPD and/or poor neonatal outcome than all survivors (Table 15). The ones with the duration of mechanical ventilation between 40% and 50% of LOS had significantly more often a proven sepsis, proven NEC, CLD, BPD and/or poor neonatal outcome. The ones whose duration of mechanical ventilation was longer than 50% of LOS had significantly more proven sepsis, CLD and/or an intracranial haemorrhage grade 3-4.

Table 15: Statistics of duration of mechanical ventilation as percentage of LOS for the mechanical ventilated survivors

Duration of mech. ventilation as % of LOS	30%-40%	40%-50%	> 50%
n	8	5	2
min GA (weeks)	25	25	25
min BW (g)	550	640	660
min LOS (days)	40	112	102
min pH-value of umbilical artery	7.13	7.15	7.33
min APGAR after 5 min	7	7	9
female	62.5%	60.0%	33.3%
multiple birth	0.0%	20.0%	0.0%
C-section	75.0%	60.0%	66.7%
SGA	25.0%	0.0%	0.0%
SHC	33.3%	40.0%	0.0%
major cong.malformation	12.5%	20.0%	0.0%
proven sepsis	25.0%	40.0%[a]	66.7%[b]
proven NEC	25.0%[c]	20.0%[b]	0.0%
CLD	75.0%[b]	100.0%[b]	100.0%[b]
BPD	75.0%[c]	60.0%[b]	33.3%
respiratory distress	100.0%	100.0%	100.0%
intracranial haemorrhage grade 3-4	0.0%	20.0%	33.3%[b]
poor neonatal outcome	75.0%[c]	80.0%[b]	33.3%

Significant difference from all survivors:
a: $p_C<0.05$
b: $p_C<0.01$
c: $p_C<0.0001$

4.5.4 CPAP treatment

4.5.4.1 Description

The frequency of the perinatal centre infants with CPAP administration increased significantly over time ($p_L<p_C<0.0001$): 48.2% in 1996, 65.1% in 2000 and 80.5% in 2004. 65.1% of the infants received a CPAP treatment (95% CI 62.9-67.3%). The minimal rate in a perinatal centre amounted to 18.0% in 1996, 44.4% in 2000, 52.1% in 2004, and on average 47.4%. The maximal rate was 78.8% in 1996, 84.3% in 2000, 88.3% in 2004, and on average 82.2%. The low frequency in 1996 can be explained with a later introduction of CPAP administration than in other hospitals.
22.0% of the infants had only a CPAP administration and no mechanical ventilation in 1996, 34.4% in 2000 and 41.7% in 2004, also a significant increase ($p_L<p_C<0.0001$). The average frequency amounted to 33.1% (95 CI 30.9-35.2%).

The frequency of CPAP administration increased in all age groups (Figure 34). For the infants with <26 completed weeks, the level rose significantly ($p_C=0.003$, $p_L<0.001$) from 42.9% in 1996 to 59.2% in 2000 and 73.8% in 2004. 63.4% of the infants with 26-27 weeks had a CPAP administration in 1996, 77.5% in 2000 and 83.9% in 2004; a significant increase ($p_C=0.02$, $p_L<0.001$). A significant difference between any two years could be observed for the infants with 28 and 29 weeks: 58.1% in 1996, 70.5% in 2000 and 88.9% in 2004 ($p_L<p_C<0.0001$). The same result was given for the infants with 30 and 31 weeks ($p_L<p_C<0.0001$): 37.4% in 1996, 57.3% in 2000 and 75.2% in 2004.
The average rate amounted to 59.4% - 10.2% with CPAP treatment only - for the infants with <26 weeks, 76.0% - 26.6% with CPAP treatment only - for the infants with 26-27 weeks, 72.6% - 37.6% with CPAP treatment only - for the infants with 28-29 weeks and 56.9% - 38.7% with CPAP treatment only - for the infants with 30-31 weeks (Figure 35). These rates didn't differ significantly between any two age groups only between the youngest age group and the children with 30-31 weeks ($p_C=0.53$),

between infants with 26-27 weeks and the ones with 28-29 weeks (p_C=0.27). All other pairs had a high significant difference (p_C<0.001).

Figure 34: Distribution of infants with CPAP treatment per different categories and per year.

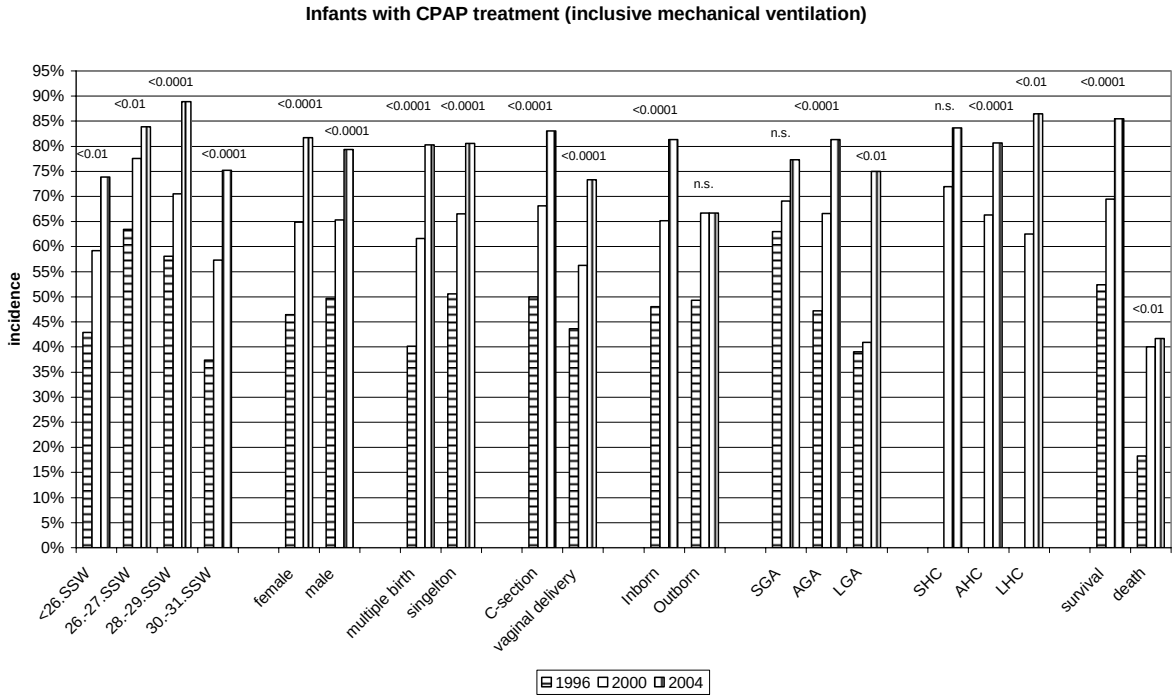
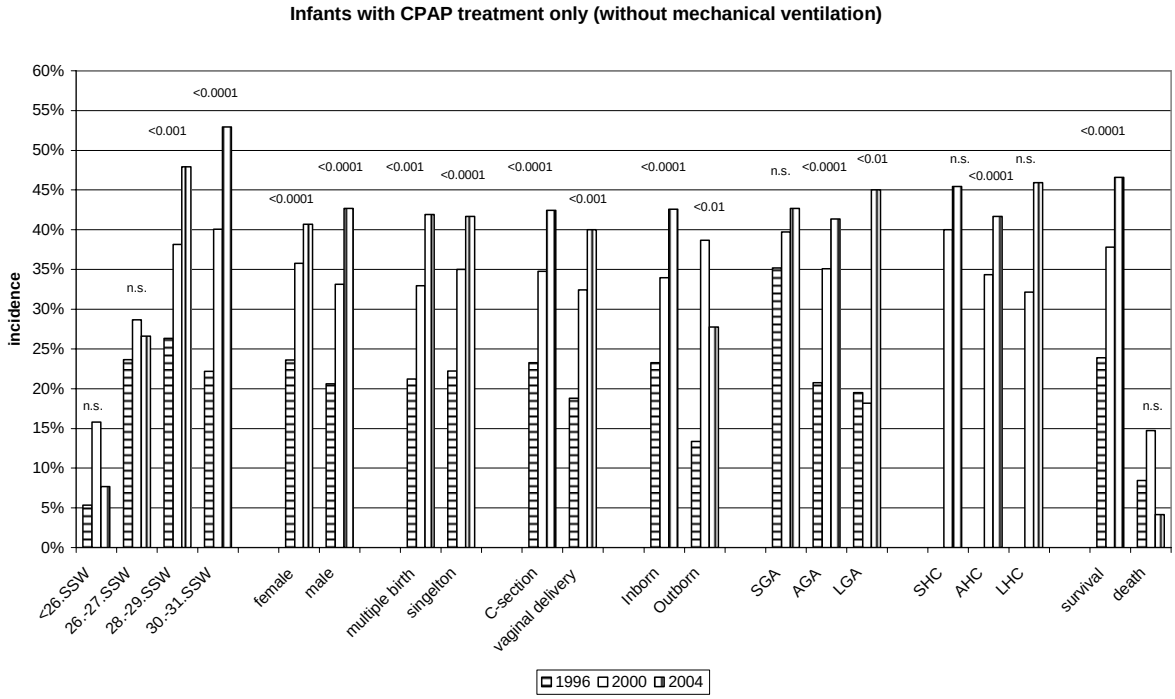


Figure 35: Distribution of infants with CPAP treatment only (no mechanical ventilation) per different categories and per year



The gender didn't have a significant different frequency of CPAP administration in any year and overall (p_C=0.44 in 1996, p_C=0.90 in 2000, p_C=0.47 in 2004, p_C=0.88 overall; female versus male OR=0.99, 95% CI 0.81-1.19). The increases for the females and males were significant. The frequency

for the first rose significantly ($p_L<p_C<0.0001$) from 46.4% in 1996 to 64.9% in 2000 and 81.7% in 2004. 49.7% of the males got CPAP treatment in 1996, 65.3% in 2000 and 79.4% in 2004; a significant difference over the year as well ($p_L<p_C<0.0001$). The average rate amounted to 64.9% - 33.7% with CPAP treatment only - for the females and 65.3% - 32.5% with CPAP only - for the males.

The increase of the rate of the multiple births with CPAP treatment from 40.2% in 1996 to 61.6% in 2000 and 80.3% in 2004 was significantly ($p_C<p_L<0.0001$). The same result was found for the singletons: 50.6% in 1996, 66.5% in 2000 and 80.6% in 2004 ($p_L<p_C<0.0001$). 63.3% - 33.4% with CPAP treatment only - of the multiple births and 65.8% - 32.9% with CPAP only - of the singletons received CPAP treatment on average. The singletons received significantly more often CPAP administration than the multiple births only in 1996 ($p_C=0.035$ in 1996, $p_C=0.24$ in 2000, $p_C=0.95$ in 2004, $p_C=0.31$ overall; multiple versus single birth OR=0.90, 95% CI 0.73-1.11).

50.0% of the infants born by C-section received CPAP treatment in 1996, 68.1% in 2000 and 83.1% in 2004 with a significant increase ($p_L<p_C<0.0001$). The frequency of vaginal delivered children increased significantly from 43.6% in 1996 to 56.3% in 2000 and 73.3% in 2004 as well ($p_C<p_L<0.0001$). The average rate was 67.9% - 34.0% with CPAP treatment only - of the children born by C-section and 57.3% - 30.0% with CPAP treatment only - of the vaginal delivered infants. The first received significantly more CPAP treatment in 2000 and 2004, and on average ($p_C=0.17$ in 1996, $p_C=0.008$ in 2000 and 2004, $p_C<0.001$ overall). The odds ratio of the children with C-section relative to the vaginal births amounted to 1.58 (95% CI 1.27-1.96).

A high significant increase of CPAP administration application was seen for the inborns ($p_L<p_C<0.0001$): 48.0% in 1996, 65.1% in 2000 and 81.3% in 2004, on average 65.8% - 33.9% with CPAP treatment only. 49.3% of the outborns got CPAP treatment in 1996, 66.7% in 2000 and 2004, and on average 59.7% - 26.3% with CPAP treatment only. Only the yearly difference between 1996 and 2000 was significantly ($p_C=0.032$, $p_L=0.040$) however not the difference over the years ($p_C=0.06$). The rates of the two groups differed only in 2004 ($p_C=0.82$ in 1996, $p_C=0.80$ in 2000, $p_C=0.030$ in 2004, $p_C=0.10$ overall; inborn versus outborn OR=1.30, 95% CI 0.95-1.77).

Only a tendency and not a significant raise ($p_C=0.20$, $p_L=0.07$) was found for the SGA infants: 63.0% in 1996, 69.1% in 2000 and 77.3% in 2004. 63.0% of the AGA children got CPAP treatment in 1996 and the rate increased significantly ($p_L<p_C<0.0001$) to 66.6% in 2000 and 81.4% in 2004. The frequency of CPAP amounted for the LGA infants to 39.0% in 1996, 40.9% in 2000 and 75.0% in 2004 with a significant difference over the years ($p_C=0.001$, $p_L=0.001$).
70.6% - 39.6% with CPAP only - of the SGA infants received CPAP administration, 65.5% - 32.7% with CPAP treatment only - of the AGA and 51.2% - 27.2% with CPAP treatment only - of the LGA children. The differences between the rates of SGA and AGA children were significantly only in 1996 ($p_C=0.027$ in 1996, $p_C=0.68$ in 2000, $p_C=0.41$ in 2004, $p_C=0.16$ overall; SGA versus AGA OR=1.26, 95% CI 0.91-1.74). A significant higher CPAP treatment rate for the AGA infants than the LGA ones was found in 2000 and overall ($p_C=0.31$ in 1996, $p_C<0.001$ in 2000, $p_C=0.32$ in 2004, $p_C=0.001$ overall). The relative risk of LGA children to get CPAP administration relative to the AGA ones amounted to 0.55 (95% CI 0.38-0.80).

The frequency of SHC infants with CPAP treatment didn't increase significantly from 72.0% in 2000 to 83.6% in 2004 ($p_C=0.16$). 66.3% of the AHC children got CPAP treatment in 2000 and 80.7% in 2004, a significant difference ($p_C<0.001$). The raise for the LCH children was significantly as well ($p_C=0.012$): 62.5% in 2000 and 86.5% in 2004. The three groups didn't have significant different frequencies of CPAP treatment (SHC versus AHC $p_C=0.32$, OR=1.28, 95% CI 0.79-2.07; LHC versus AHC $p_C=0.75$, OR=0.92, 95% CI 0.58-1.48). 42.9% of the SHC children received on average with CPAP treatment only, 38.1% of the AHC ones and 37.6% of the LHC ones.

The survivors got significantly more CPAP treatment over time ($p_L<p_C<0.0001$): 52.4% in 1996, 69.5% in 2000, 85.5% in 2004, and on average 69.7% - 36.5% with CPAP treatment only. For the infants who died in a perinatal centre and got CPAP treatment, the increase from 18.3% in 1996 to 40.0% in 2000 respectively 41.7% in 2004 was significantly ($p_C=0.004$, $p_L=0.003$) with an average rate of 34.0% - 9.7% with CPAP treatment only.

4.5.4.2 The mortality rate

4.7% of the infants with CPAP treatment died in 1996, 9.0% in 2000 and 5.9% in 2004. The rates didn't differ over the years ($p_C=0.05$) although the yearly change between 1996 and 2000 was significantly ($p_C=0.032$). The mortality rate of the infants without CPAP administratoin amounted to 19.5% in 1996, 25.3% in 2000 and 34.1% in 2004; a significant different increase over the years ($p_C=0.006$). The average mortality rate was 6.7% (95% CI 5.3-8.2%) for the infants with CPAP treatment and 24.3% (95% CI 21.0-27.7%) for the others. The latter group died significantly more frequently ($p_C<0.001$ in any year and overall). The odds ratio of the children with CPAP treatment relative to the ones without CPAP treatment amounted to 0.22 (95% CI 0.17-0.30).

The infants who suffered from RDS and were treated with CPAP treatment had a significant lower mortality rate than those without the therapy ($p_C<0.0001$; OR 0.14, 95% CI 0.11-0.20). 3.9% of the ventilated children died in 1996, 9.7% in 2000, 5.7% in 2004 – a significant change over the years ($p_C=0.008$) - and on average 6.7%. The mortality rate of the non-treated infants amounted to 23.9% in 1996, 38.9% in 2000, 48% in 2004 – a significant linear increase ($p_C<0.001$, $p_L<0.0001$) – and on average 33.1%. Also the CPAP treatment -ventilated infants with CLD died significantly less often ($p_C<0.001$; OR 0.21, 95% CI 0.08-0.53).; 0.9% in 1996, 4.2% in 2000, 2.6% in 2004 – no significant change ($p_C=0.25$) - and on average 2.7%. The mortality rate of the non-ventilated children with a CLD was 7.7% in 1996, 20.0% in 2000, 33.3% in 2004 – no consistent significant increase ($p_C=0.12$, $p_L=0.043$) – and on average 11.8%. Due to a low frequency of children with BPD and without CPAP administration, the ventilated infants had a significant lower risk to died than the non-ventilated ones ($p_C<0.001$; OR 0.09, 95% CI 0.02-0.42). For the first, the mortality rate was 2.0% in 1996, 1.6% in 2000, 1.2% in 2004 – no significant decrease ($p_C=0.94$, $p_L=0.72$) – with an average rate of 1.5%. 17.4% of the non-ventilated children with BPD died in 1996, none in 2000 and 2004 – no significant change ($p_C=0.66$) – and on average 14.8%.

The mortality rate of the children who only received CPAP treatment and no mechanical ventilation amounted to 4.8% in 1996, 6.3% in 2000, 1.1% in 2004, and on average 3.8% (95% CI 2.3%-5.3%). These infants died significantly less than the infants who received CPAP administration and mechanical ventilation ($p_C=0.010$, OR=0.54, 95% CI 0.34-0.87).

4.5.4.3 The duration of CPAP treatment

The mean duration of CPAP treatment of the 1122 survivors who received CPAP administration amounted to 10.2 days in 1996 and increased to 14.9 days in 2000 and 16.9 days in 2004 (Figure 36). This increase wasn't consistently significantly ($p_C=0.27$, $p_L<0.0001$). The mean duration of CPAP administration for all survivors was 14.7 days (95% CI 13.6-15.7 days). 90% of the infants were mechanical ventilated shorter than 32 days in 1996, 42 days in 2000 and 48 days in 2004. 50% of those survivors had CPAP treatment up to approximately 5 days in 1996, 7 days in 2000 and 2004, and on average 6.5 days. 90% of those survivors ended the CPAP treatment before 31.5 days in 1996, 42 days in 2000 and 48 days in 2004; on average 42 days.

The minimal mean duration of CPAP administration in one of the perinatal centres was 4.1 days in 1996, 5.2 days in 2000, 6.3 days in 2004 with an average mean duration of 6.7 days. The maximal

mean duration in one of the perinatal centres was 14.1 days in 1996, 25.5 days in 2000, 32.1 days in 2004, and on average 25.7 days.

Figure 36: Cumulative curve of survivors with CPAP treatment per year.

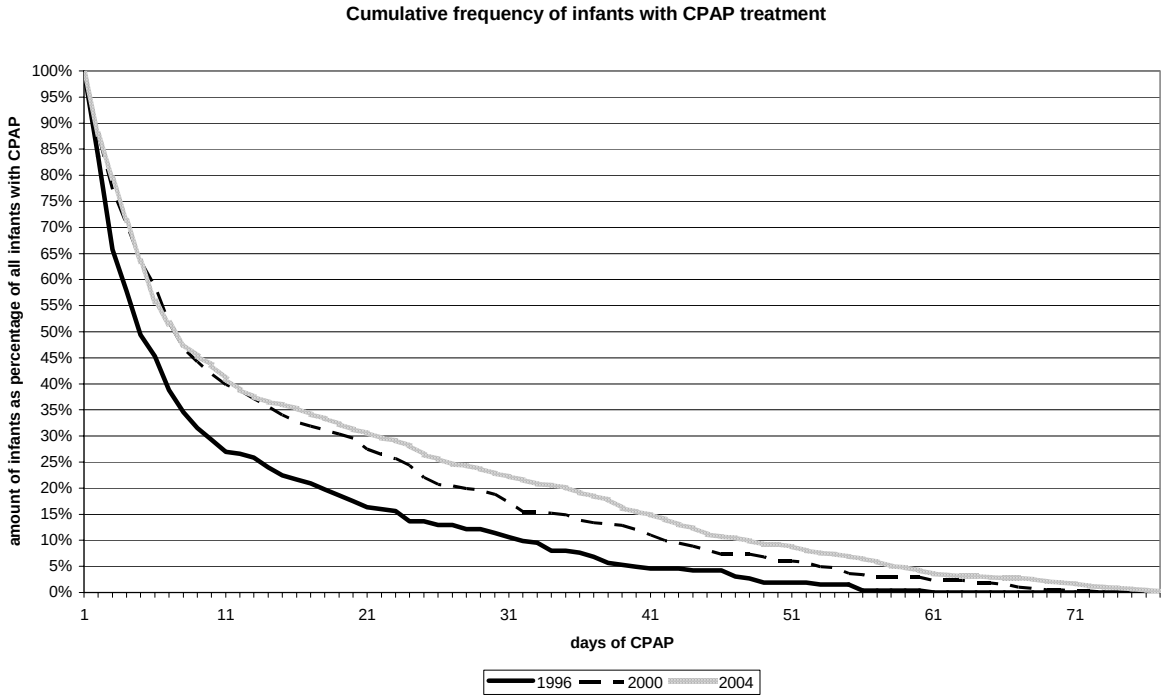


Table 16: Statistics of duration of CPAP treatment as percentage of LOS for the CPAP treated survivors

CPAP treatment as % of LOS	60%-70%	70%-80%	> 80%
n	24	14	5
min GA (weeks)	24.6	25.4	26.1
min BW (g)	600	650	590
min LOS (days)	48	47	48
min pH-value of umbilical artery	6.86	6.92	7.15
min APGAR after 5 min	5	1	7
female	58.3%	50.0%	60.0%
multiple birth	29.2%	21.4%	0.0%
C-section	91.7%	78.6%	80.0%
SGA	12.5%	21.4%	40.0%[a]
SHC	19.0%[a]	14.3%	20.0%
major cong.malformation	0.0%	0.0%	20.0%
proven sepsis	33.3%[b]	35.7%[b]	0.0%
proven NEC	8.3%	0.0%	0.0%
CLD	58.3%[b]	42.9%[b]	60.0%
BPD	29.2%[a]	14.3%	20.0%
respiratory distress	91.7%	92.9%	60.0%
intracranial haemorrhage grade 3-4	4.3%	7.7%	0.0%
poor neonatal outcome	29.2%	28.6%	0.0%

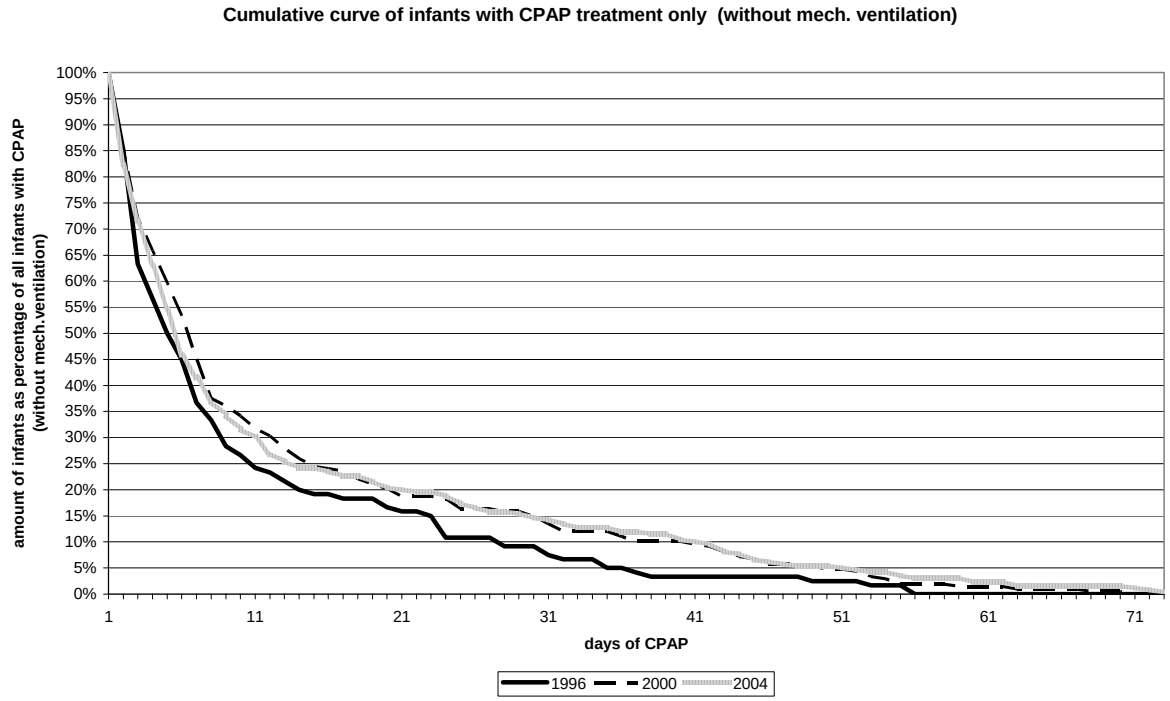
Significant difference from all survivors:
a: $p_C<0.05$
b: $p_C<0.01$
c: $p_C<0.0001$

For the CPAP treated survivors, the duration of the CPAP administration as percentage of the length of stay varied between 0.7% and 90.3%. 50% of those infants had the duration of CPAP treatment up to

11.1% of the LOS and 90% up to 49.2% of LOS. The survivors with a duration of CPAP administration between 60% and 70% of LOS had significantly more often a proven sepsis, CLD and/or BPD than all survivors (Table 16); they were significantly more often examined for their head circumference. The ones with the duration of CPAP treatment between 70% and 80% of LOS had significantly more frequently a proven sepsis and/or CLD; the ones whose duration of CPAP treatment was longer than 85% of LOS were significantly smaller for their gestational age than all survivors.

588 survivors had only a CPAP treatment and no mechanical ventilation. For these infants, the mean duration of CPAP administration amounted to 9.3 days in 1996, 12.2 days in 2000, 12.4 days in 2004 (Figure 37). The duration didn't differ significantly over the years (p_C=0.36, p_L=0.11). The average mean duration of CPAP administration amounted to 11.7 days (95% CI 10.5-12.9 days). 50% of those survivors ended CPAP treatment before 5 days in 1996, 6.5 days in 2000, 5.5 days in 2004, and on average 5.5 days. 90% had CPAP treatment up to 27.5 days in 1996, 40 days in 2000, 41 days in 2004, and on average 36 days.

Figure 37: Cumulative survivors with CPAP treatment only per year.



4.5.5 Respiratory support

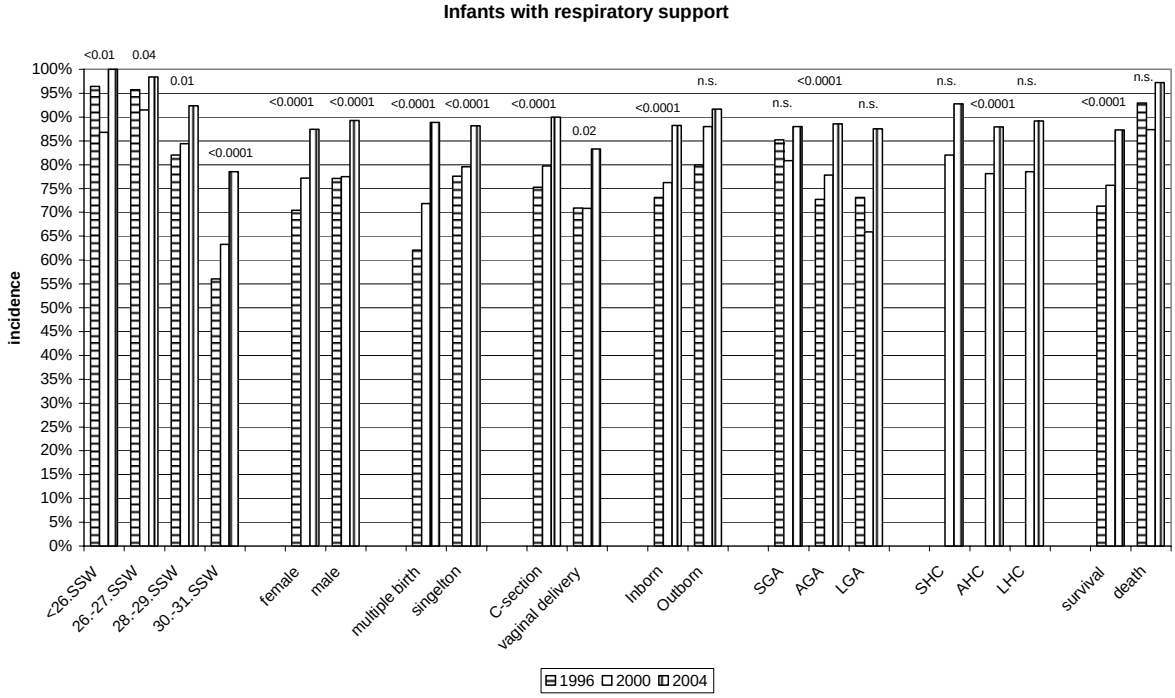
Respiratory support is defined as mechanical ventilation and/or CPAP treatment. The duration is calculated by adding the duration of both ventilation types. 74.0% of the infants delivered to a perinatal centre got a respiratory support in 1996, 77.4% in 2000 and 88.4% in 2004. The average rate amounted to 80.1% (95% CI 78.3-81.9%). The rates differed significantly over the years ($p_C<p_L<0.0001$). The minimal rate in the perinatal centres was 48.0% in 1996, 55.6% in 2000, 68.8% in 2004, and on average 60.3%. The maximal rate amounted to 88.5% in 1996, 92.9% in 2000, 97.9% in 2004, and on average 92.4%.

96.4% of the infants with <26 completed weeks received a respiratory support in 1996, 86.8% in 2000 and 100.0% in 2004 (Figure 38); significant differences over the years (p_C=0.003). A similar result was found for the infants with 26 -27 weeks: 95.7% in 1996, 91.5% in 2000 and 98.4% in 2004; significant differences over the years (p_C=0.037). The frequency of infants with 28-29 weeks who got respiratory

support increased significantly from 82.0% in 1996 to 84.4% in 2000 and 92.4% in 2004 (p_C=0.014, p_L=0.006). A significant raise could be calculated for the infants with 30-31 weeks: 56.0% in 1996, 63.3% in 2000 and 78.5% in 2004 ($p_L<p_C$<0.0001).
The average frequency of respiratory support amounted to 93.9% for youngest age group, 95.1% for the infants with 26-27 weeks, 86.3% for the infants with 28-29 weeks, and 66.1% for the oldest age group. The rates didn't differ significantly between the youngest two age groups only (p_C=0.55). All other pairs of age group were significantly i.e. the application of respiratory support decreased with gestational age (p_C=0.005 between the infants with <26 weeks and the infants with 28-29 weeks; p_C<0.001 the rest of the pairs of age group).

The frequency of respiratory support for the females increased significantly ($p_L<p_C$<0.0001) over the years from 70.4% in 1996 to 77.2% in 2000 and 87.5% in 2004 with an average rate of 78.6%. A raise of the application of respiratory support was seen for the males as well ($p_L<p_C$<0.0001): 77.1% in 1996, 77.5% in 2000, 89.3% in 2004, and on average 81.4%. The rate didn't differ significantly between the gender in all years and overall (p_C=0.07 in 1996, p_C=0.92 in 2000, p_C=0.48 in 2004, p_C=0.12 overall; female versus male OR=0.84, 95% CI 0.67-1.05).

Figure 38: Distribution of infants with respiratory support per different categories and per year.



The singletons got significantly more frequently a respiratory support than the multiple births (p_C<0.001 in 1996, p_C=0.036 in 2000, p_C=0.81 in 2004, p_C=0.005 overall). The odds ratio of the multiple births relative to the single ones amounted to 0.71 (95% CI 0.55-0.90). 62.1% of the multiple births received respiratory support in 1996, 71.9% in 2000, 88.9% in 2004, and on average 75.9; a significant increase ($p_C<p_L$<0.0001). The rates for the singletons increased significantly ($p_C<p_L$<0.0001) as well from 77.6% in 1996 to 79.6% in 2000 and 88.2% in 2004 with an average rate of 81.7%.

The infants born by C-section received significantly more often a mechanical or CPAP treatment than vaginal births (p_C=0.28 in 1996, p_C=0.023 in 2000, p_C=0.026 in 2004, p_C<0.001 overall). The relative risk of the children born by C-section relative to the others was 1.52 (95% CI 1.19-1.96). 75.2% of the first in 1996 and this rate increased significantly ($p_L<p_C$<0.0001) to 79.7% in 2000 and 90.0% in 2004.

The frequency of the vaginal born infants with respiratory support amounted to 70.9% in 1996 and 2000 and increased significantly (p_C=0.015, p_L=0.012) to 83.3% in 2004. The average rate was 82.0% for the children born by C-section and 74.9% for the vaginal births.

The frequency of the inborns with respiratory support rose significantly ($p_L<p_C<0.0001$) from 73.1% in 1996 to 76.2% in 2000 and 88.2% in 2004 with an average rate of 79.6%. A stable level of respiratory support was found for the outborns (p_C=0.19, p_L=0.08): 80.0% in 1996, 88.0% in 2000, 91.7% in 2004, and on average 85.5%. The rates of the two groups differed significantly only in 2000 (p_C=0.20 in 1996, p_C=0.022 in 2000, p_C=0.52 in 2004, p_C=0.05 overall; inborn versus outborn OR=0.66, 95% CI 0.43-1.01).

The SGA infants received a constant level of respiratory support (p_C=0.49): 85.2% in 1996, 80.9% in 2000 and 88.0% in 2004. An increase was found for AGA children ($p_L<p_C<0.0001$): from 72.7% in 1996 to 77.9% in 2000 and 88.5% in 2004. 73.2% of the LGA infants had respiratory support in 1996, 65.9% in 2000 and 87.5% in 2004; a significant difference only between 2000 and 2004 (p_C=0.021) with no significant different rates over the years (p_C=0.07).
The average rates amounted to 84.8% for the SGA, 79.9% for the AGA and 75.2% for the LGA infants. The SGA infants received significantly more frequently a ventilation than the AGA ones only in 1996 (p_C=0.049 in 1996, p_C=0.57 in 2000, p_C=0.88 in 2004, p_C=0.10 overall; OR=1.40, 95% CI 0.93-2.11). No significant difference between the rates of the AGA and LGA infants were observed in any year and on average (p_C=0.94 in 1996, p_C=0.07 in 2000, p_C=0.84 in 2004, p_C=0.21 overall; LGA versus AGA OR=0.76, 95% CI 0.50-1.17).

The frequency of SHC infants with respiratory support tended to rise from 82.0% in 2000 to 92.7% in 2004, however not significantly (p_C=0.10), with an average rate of 87.6%. For the AHC children, the increase from 78.1% to 87.9% was highly significantly ($p_C<0.0001$). The average rate amounted to 83.1%. 78.6% of the LHC infants got a respiratory support in 2000, 89.2% in 2004, and on average 82.8%; no significant increase (p_C=0.18). The three groups didn't have significant different rates CPAP treatment. The odds ratio of the SHC children relative to the AHC ones amounted to 1.44 (p_C=0.24, 95% CI 0.79-2.63). The relative risk of the LHC infants relative to the AHC ones was 0.98 (p=0.93; 95% CI 0.56-1.72).

The rate increased from 71.3% in 1996 to 75.6% in 2000 and 87.3% in 2004 was significantly for the survivors ($p_C<0.0001$). 93.0% of the infants who died in a perinatal centre received respiratory support in 1996, 87.4% in 2000 and 97.2% in 2004, a significant change only between 2000 and 2004 (p_C=0.024) with no significant difference over the years (p_C=0.06). The average rate amounted to 78.3% for the survivors and 92.0% for the dying infants.

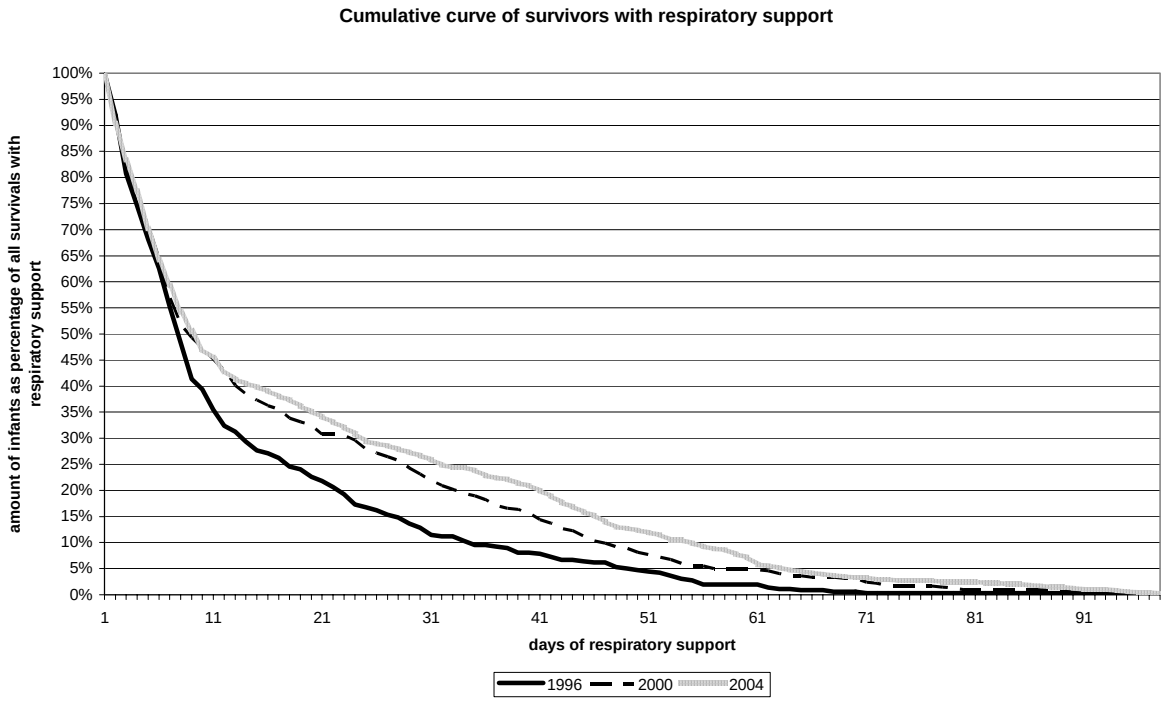
4.5.5.1 The mortality rate

The mortality rate of the infants with respiratory support was 15.6% in 1996, 16.6% in 2000, 12.6% in 2004, and on average 14.8% (95% CI 13.0-16.6%). No clear tendency could be found over the years (p_C=0.15). No significant differences (p_C=0.10) of the mortality rates were observed for the children without respiratory support: 3.4% in 1996, 8.2% in 2000, 2.7% in 2004 (p_C=0.07 between 1996 and 2000, p_C=0.11 between 2000 and 2004, p_C=0.81 between 1996 and 2004), and on average 5.2% (95% CI 2.9-7.4%). Obviously, the rates differed significantly between the two groups in all years and on average ($p_C<0.001$ in 1996, p_C=0.012 in 2000, p_C=0.014 in 2004, $p_C<0.001$ overall). The children with respiratory support had a three times higher risk to die than the ones without respiratory support (OR=3.19, 95% CI 1.97-5.17).

4.5.5.2 The duration of respiratory support

The mean duration of a respiratory support (Figure 39) amounted for the 1261 survivors with at least one day of respiratory support to 13.2 days in 1996, 17.6 days in 2000, 19.8 days in 2004, and on average 17.2 days (95% CI 16.1-18.3 days). This increase wasn't consistently significantly (p_C=0.60, p_L<0.0001). 90% of the infants had a respiratory support shorter than 34 days in 1996, 47 days in 2000 and 55 days in 2004.

Figure 39: Cumulative curve of survivors with respiratory support per year.



The minimal mean duration of respiratory support in one of the perinatal centres was 8.4 days in 1996, 10.8 days in 2000, 8.4 days in 2004 with an average mean duration of 10.7 days. The maximal mean duration in one of the perinatal centres was 17.8 days in 1996, 27.4 days in 2000, 33.0 days in 2004, and on average 24.4 days.

4.5.6 Surgery

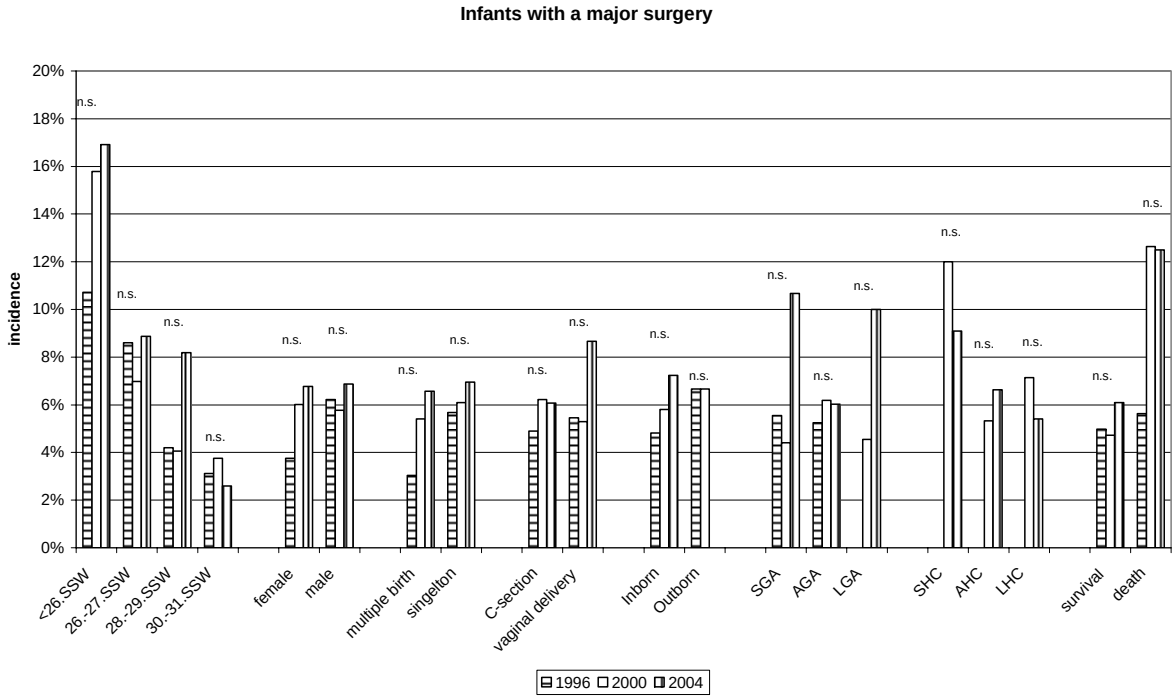
4.5.6.1 Description

Only few of the infants in a perinatal centre had to have a major surgery: 5.1% in 1996, 5.9% in 2000 and 6.8% in 2004. The average frequency amounted to 6.0% (95% CI 4.9-7.0%). The increase wasn't significantly at all (p_C=0.43, p_L=0.20). The minimal rate in a perinatal centre was 1.2% in 1996, 0% in 2000, and 2.0% in 2004 with an average rate of 2.1%. The maximal frequency was 10.9% in 1996, 11.1% in 2000, 12.3% in 2004, and on average 9.3%.

A rising trend of a major surgery (Figure 40) was found for the youngest age group (p_C=0.60, p_L=0.35): 10.7% in 1996, 15.8% in 2000 and 16.9% in 2004. 8.6% of the infants with 26-27 completed weeks had a major surgery in 1996, 7.0% in 2000 and 8.9% in 2004 with no significant different rates over the years (p_C=0.84). The frequency of children with 28-29 weeks tended to remain stable as well (p_C=0.16): 4.2% in 1996, 4.0% in 2000 and 8.2% in 2004. The same result was seen for the oldest age group (p_C=0.75): the rates varied between 3.1% in 1996, 3.7% in 2000 and 2.6% in 2004.

The average frequencies decreased with the gestational age: 14.7% for the infants with <26 weeks, 8.1% for the ones with 26-27 weeks, 5.5% for the ones with 28-29 weeks and 3.1% for the oldest age group. The only non-significant difference was observed for the rates of the middle two age groups (p_C=0.016 between infants with <26 weeks and the ones with 26-27 weeks, p_C<0.001 for the infants with <26 weeks and the ones with 28-29 weeks respectively 30-31 weeks, p_C=0.13 between infants with 26-27 weeks and the ones with 28-29 weeks, p_C<0.001 between infants with 26-27 weeks and infants 30-31 weeks, p_C=0.039 between infants with 28-29 weeks and the ones with 30-31 weeks).

Figure 40: Distribution of infants with a major surgery per different categories and per year.



A rising tendency of major surgeries could be found for the females (p_C=0.27, p_L=0.12): 3.7% in 1996, 6.0% in 2000, 6.8% in 2004, and on average 5.6%. The frequency of males who had a major surgery tended to remain stable (p_C=0.84) at the level of 6.2% in 1996, 5.8% in 2000 and 6.9% in 2004 with an average rate of 6.3%. The gender didn't differ in the frequencies at all (p_C=0.18 in 1996, p_C=0.89 in 2000, p_C=0.97 in 2004, p_C=0.52 overall; female versus male OR=0.88, 95% CI 0.60-1.30).

The same result was seen for the single and multiple births. 3.0% of the multiple births had a major surgery in 1996, 5.4% in 2000, 6.6% in 2004 (p_C=0.37, p_L=0.17) and 5.2% on average. The frequency of the singletons with a major surgery amounted to 5.7% in 1996, 6.1% in 2000, 6.9% in 2004 (p_C=0.73, p_L=0.44), and on average 6.2% (p_C=0.80 between 1996 and 2000, p_C=0.61 between 2000 and 2004, p_C=0.44 between 1996 and 2004). The two groups didn't have significant different rates (p_C=0.22 in 1996, p_C=0.74 in 2000, p_C=0.86 in 2004, p_C=0.42 overall; multiple versus single births OR=0.83, 95% CI 0.53-1.30).

A stable rate for the infants born by C-section was found as well (p_C=0.67): 4.9% in 1996, 6.2% in 2000, and 6.1% in 2004 with an average rate of 5.8%. The frequency of vaginal births with a major surgery was 5.5% in 1996, 5.3% in 2000, 8.7% in 2004, and on average 6.4%; no significant differences over the years (p_C=0.40). The rates for the two mode of delivery didn't differ significantly (p_C=0.80 in 1996, p_C=0.67 in 2000, p_C=0.26 in 2004, p_C=0.60 overall; C-section versus vaginal births OR=0.89, 95% CI 0.58-2.20).

The inborns had an increasing trend of major surgeries (p_C=0.24, p_L=0.09): 4.8% in 1996, 5.8% in 2000 and 7.2% in 2004 with an average rate of 6.0% rates. For the outborns, 6.7% major surgeries were only reported in 1996 and 2000 (p_C=0.28). The group rates didn't differ significantly (p_C=0.50 in 1996, p_C=0.75 in 2000, p_C=0.09 in 2004, p_C=0.72 overall; inborn versus outborn OR=1.13, 95% CI 0.58-2.20).

No significance rate differences over the years (p_C=0.30) were seen for the SGA infants: 5.6% in 1996, 4.4% in 2000, 10.7% in 2004, and on average 7.1%. 5.2% of the AGA children had a major surgery in 1996, 6.2% in 2000, 6.0% in 2004 with an average rate of 5.8%; no significant difference either (p_C=0.79). No LGA infant had a major surgery in 1996, 4.5% in 2000 and 10.0% in 2004, a significant difference only between 1996 and 2004 (p_C=0.040) however not consistently over the years (p_C=0.11, p_L=0.036). The average frequency amounted to 4.8%. The three groups didn't have any significant different rate of major surgeries (SGA versus AGA p_C=0.48, OR=1.23, 95% CI 0.69-2.21; LGA versus AGA p_C=0.63, OR=0.81, 95% CI 0.35-1.90).

12.0% of the SHC infants had a major surgery in 2000, 9.1% in 2004 – no significant decrease over the years (p_C=0.61). The raise of the AHC children from 5.4% to 6.6% wasn't significantly either (p_C=0.37). No significant decrease was found for the LHC infants (p_C=0.74): 7.1% in 2000, 5.4% in 2004. The average rate amounted to 10.5% for the SHC, 6.0% for the AHC and 6.5% for the LHC infants. The frequencies of the three groups didn't differ significantly (SHC versus AHC p=0.07, OR=1.84, 95% CI 0.93-3.61; LHC versus AHC p=0.86, OR=1.08, 95% CI 0.46-2.57).

The frequencies of the survivors with a major surgery remained stable (p_C=0.56): 5.0% in 1996, 4.7% in 2000 and 6.1% in 2004 with an average rate of 5.3%. For the infants who died in a perinatal centre and had a major surgery, the increase from 5.6% in 1996 to 12.6% in 2000 respectively 12.5% in 2004 wasn't significantly (p_C=0.28). The average rate amounted to 10.5%.

4.5.6.2 The mortality rate

The mortality rate of the infants who were delivered to a perinatal centre and had a major surgery amounted to 13.8% in 1996, 31.6% in 2000, 20.9% in 2004, and on average 22.7% (95% CI 14.8-30.7%). The changes over the years weren't significantly (p_C=0.21). The mortality rate for the children with no or a minor surgery tended to remain stable (p_C=0.30): 12.3% in 1996, 13.7% in 2000, 10.7% in 2004, and on average 12.3% (95% CI 10.7-13.8%). The average rate for the latter was 12.3%. A significant different mortality rate between the two groups were found in 2000, 2004 and overall (p_C=0.82 in 1996, p_C=0.003 in 2000, p_C=0.042 in 2004, p_C=0.02 overall). The children with a major surgery had twice the risk to die than the other infants (OR=2.11, 95% CI 1.32-3.36).

4.6 International studies

In this chapter, the study results of European, American and Australian/New Zealand very preterm infants will be compared.

4.6.1 The MOSAIC study

The Models of Organizing Access to Intensive care for Very Preterm Births (MOSAIC) study [85] covered 494'463 total very preterm infants who were born alive between 24 and 31 weeks without lethal congenital anomalies in 10 European regions in 2003. The rate of very preterm live births amounted to 9.9‰ in Europe and was similar to the one in Switzerland (9.0‰) in 2004 (Table 17). The frequency of female tended to be the same in all countries. The gestational age didn't differ significantly in the European regions and tended to be lower than in Switzerland (28.6 weeks and 29.1

weeks, respectively). Mean birth weights were significantly higher in Poland and Netherlands and lower in France (1245g, 1244g and 1185g, respectively) than the European average (1208g). The one of Swiss very preterm infant (1217g) didn't differ significantly from the average. After standardization on gestational age and gender, Hesse and the Northern region in the UK had significantly lower mortality rates than the European average (7.3% and 9.2%, respectively), and the Netherlands and the Polish regions had significantly higher ones (21.4% and 21.5%, respectively). Comparing the crude in-hospital mortality rates, the German region had a significant lower mortality rate than Switzerland (7.9% and 11.4%, respectively). Significantly more infants died in Flanders, Lazio and in the Poland regions (16.0%, 17.6% and 24.7%, respectively) than in Switzerland.

Table 17: Birth rate, mean gestational age and birth weight, rate of female and in-hospital mortality rate of very preterm live-births.

Region (Country)	Very preterm birth rate (‰)	Mean gestational age (weeks)	Mean birth weight (g)	Female (%)	In-hospital mortality rate (%)
Flanders (Belgium)	9.1	28.6	1195	42	16.0[b] (13.1-19.4)
Eastern region of Denmark	9.5	28.7	1234	47	10.8 (7.7-14.7)
Ile-de-France (France)	10.2	28.7	1185	48	14.8 (12.5-17.3)
Hesse (Germany)	11.5	28.5	1198	45	7.9[b] (5.8-10.3)
Lazio (Italy)	8.4	28.7	1227	49	17.6[c] (14.2-21.5)
Eastern and Central Netherlands	7.6	29.1	1244	47	15.7 (12.1-19.8)
Wielkopolks/Lubuskie (Poland)	8.8	28.4	1245	48	24.7[d] (20.5-29.4)
Northern Portugal	7.7	28.5	1178	44	15.9 (11.7-20.8)
Northern United Kingdom	13.1	28.4	1203	43	11.8 (9.6-14.5)
Trent (United Kingdom)	13.0	28.7	1206	48	10.4 (7.6-13.2)
MOSAIC (all regions)	9.9	28.6	1208	46	14.2 (13.2-15.2)
Switzerland (year 2004)	9.0[a]	29.1	1217	47	11.4 (8.9-13.9)

a: based on BfS tables
Significant levels: Switzerland versus. other country
b:<0.05
c:<0.01
d:<0.0001

Table 18: Rates of Neurologic and Respiratory Morbidity per very preterm infants who survived to discharge.

Region (Country)	Neurologic morbidity[a]	Respiratory morbidity[b]
Flanders (Belgium)	9.3[c]	14.1
Eastern region of Denmark	2.6[c]	10.3[c]
Ile-de-France (France)	3.9	14.0
Hesse (Germany)	7.6	18.8
Lazio (Italy)	11.8[d]	9.5[c]
Eastern and Central Netherlands	5.9	11.1
Wielkopolks/Lubuskie (Poland)	15.7[e]	15.7
Northern Portugal	7.9	12.0
Northern United Kingdom	7.7	25.2[d]
Trent (United Kingdom)	6.1	21.2[d]
MOSAIC (all regions)	7.4	15.8
Switzerland (year 2004)	5.9	14.9

a: defined as Intraventricular haemorrhage (IVH) grade 3-4 or cystic Leucomalacia (PVL)
b: defined as Bronchopulmonary dysplasia (BPD)
Significant levels: Switzerland versus other country
c:<0.05
d:<0.01
e:<0.0001

Regarding only the survivors to discharge, the neurological and respiratory morbidities (Table 18) didn't differ significantly between Switzerland (5.9% and 14.9%, respectively) and the European regions (7.4% and 15.8%, respectively). The first was defined as the intraventricular haemorrhage

(IVH) grade 3-4 or cystic periventricular leucomalacia (PVL), the latter as bronchopulmonary dysplasia (BPD). There are significant differences within the single European regions: The eastern region of Denmark had significant lower rates in neurologic and respiratory morbidity (2.6% and 10.3%, respectively) than Switzerland. Flanders and the Poland region had a significant higher incidence of neurologic morbidity (9.3% and 15.7%, respectively). Lazio was observed to have a significant higher neurologic morbidity (9.3%) however a significant lower rate of BPD (9.5%) than Switzerland. The Northern United Kingdom and Trent had significant higher incidences of respiratory morbidity (25.2% and 21.2%, respectively) than Switzerland. It was argued, that the variability in morbidity could result from different diagnostic practices.

4.6.2 Rate of very preterm and very low birth weight infants

Buitendijk [18] provides a good overview of European countries. The amount of reported very preterm infants varied in Europe between 0.19% in Luxembourg and 1.40% in Austria (Table 19).

On average, approximately 1% of the liveborns are born before 32 completed gestational weeks; the Swiss frequency of very preterm infants reached with 0.83% the same level as the other European countries. The amount of stillbirths varied many more between the countries, most likely due to the definition[26] and/or lack of reporting regarding different inclusion criteria. The lowest rate was seen in Austria with 0.36% stillbirths and the highest was reported by the Greece with 2.61%; the Swiss deaths in delivery room amounted to 0.02%. Children with less than 500g constituted only a fraction of less than 0.06% of all liveborns except Ireland which reported 0.30%. A reason for that high number wasn't provided by the authors of the publication. The rate of infants with a birth weight 500-1499g was comparable to the rate of very preterm infants.

[26] The results are consistent with the study of Lack [21].

Table 19:Rate of liveborns, stillbirths and very preterm infants [18, 19][27]:

Country	Data source	year	Data provided for fetal deaths	total births	liveborns	stillbirths	very preterm(%)	<500g	500-1499g
Austria	Statistics Austria	2001	>=22w	75707	75433	0.36%	1.40%	0.03%	1.06%
Belgium (Flanders)	Studiecentrum voor Pernatale Epidemiologie	2000	>=22w, >=500g	62122	61844	0.45%	0.96%	n.a.	0.90%
Denmark	Danish perinatal database	2000	>=28w	67337	67084	0.38%	0.97%		
Finland	Medical birth registry – STAKES	2000	>=22w	56768	56541	0.40%	0.89%	0.03%	0.73%
France	INSEE	2000	>=28w	778341	774782	0.46%	0.76%	0.00%[d]	0.78%[d]
Germany (9 Bundesländer)	BAX – perinatal survey	2000 (Hessen 2001)	>=22w	557948	770744[e]		1.15%	0.05%[e]	1.05%[e]
Greece (perinatal survey)	Population based perinatal survey undertaken in 1998	1998	>=22w	14659	14277	2.61%	0.88%	0.02%	0.96%
Ireland	National Perinatal Reporting System	1999	>=22, >=500g	54302			0.94%	n.a.	0.65%
Italy	ISTAT, Civil birth and death registration. Discontinued in 1998	1998	>=180d	533624	531650	0.37%	0.87%		
Luxembourg	FIMENA 2000	2000	>=22w	5430	5696[f]		0.19%	0.02%	0.02%
The Netherlands	Merged database from professional registers (LVR, LNR)	1999	>=22w	201600	200115	0.74%	1.09%	0.04%	0.99%
Portugal	Estatisticas Demograficas, Estatisticas de Saude, Instituto Nacional de Estatistica (INE)	1999	>=22w	120861	120071	0.65%	0.84%	0.01%	0.95%
Spain (Madrid, Valencia, Pais Vasco)	Spanish Society of Neonatology	2000	>=22w	86656	85478	1.36%	0.73%	n.a.	1.22%
Sweden	Medical Birth Register	2000	>=28w	89722	89377	0.38%	0.92%	0.02%	0.75%
UK (Scotland)	Information and Statistics Division, SMR2 Maternity Discharge Sheet	2000	>=24w	52413	52115		1.23%	0.06%	1.18%
Switzerland	MNDS	2000	<32w, <1500g		78458[a]	0.02%	0.83%	0.02%	0.74%
Australia, New Zealand	Australian and New Zealand Neonatal Network (ANZNN)	1996	<32w, <1500g		307000[c]		1.96%	0.02%	1.68%[b,c]

[27] Footnotes of the table

a: provided by Swiss Federal Statistical Office

b: Darlow [20] stated liveborns <1500g as 0.96% of all New Zealand liveborns

c: Live births in Australia and New Zealand are approximate values provided by Donoghue [19]; percentage of infants with <500g respectively 500-1499g are calculated based on those approx. values

d: Data of the year 1998

e: Data from Federal bureau of statistics Wiesbaden of the year 1999

f: Data from National Statistics on Cause of Death of the year 2000

4.6.3 Comparison by gestational age

Only a few international publications were found in the Medline database that can be used for a comparison with the Swiss data. Studies were included that used the gestational age (very preterm) as inclusion criteria in this chapter and the birth weight (<1500g) in the next chapter. Also the year of the data should be comparable to the years that were examined in this thesis.

The rate of female infants was similar in all the publications and reached almost 50% (Table 20). The frequency of multiple births and C-section varied significantly between the countries. Switzerland had significantly more singletons than Netherlands and New Zealand. C-section was significantly more common in Swiss hospitals (71%) than in the other countries. The incidence of SGA children was astonishingly high in Sweden (30%).

The neonatal mortality rate was the same in Switzerland (almost 11%) as in Netherlands, except for the early and late neonatal mortality that can't be explained. New Zealand reported a significant lower mortality rate (9% versus 12%).
No clear pattern of difference can be found for the morbidities between the publications. The differences of the incidence of some morbidities between Switzerland and the other countries can be explained by a different definition of the morbidity entities. Therefore in Switzerland, the rate of congenital malformation (7%) was lower, the one of PDA (17%) and proven sepsis (10%) was higher than in the other countries that analysed the specific morbidity.
The application of antenatal steroids was more common in Netherlands and significantly higher in Australia/New Zealand (almost 80%) than in Switzerland (64%). Surfactant was given 30% in Switzerland and therefore significantly less frequently than in the other countries (40% in Netherlands and New Zealand, 56% in ANZNN). Also the infants were mechanical ventilated less frequently in Switzerland (52%) than in Netherlands (75%) and in New Zealand (92%). The frequency of CPAP treatment was the same in Switzerland as in ANZNN (almost 50%). The Swiss very preterm survivors were discharged home after 67 days, the Netherlands ones after 44 days.

The Epibel study included only the infants with less than 27 completed gestational weeks. Therefore no direct comparison is possible. Interestingly the Epibel study reported that only 303 children of 525 births were admitted to the perinatal centre - 91% of the reported infants died after the onset of labour or immediately at birth and 9% in the delivery room. 71% of the infants admitted to the perinatal centres survived the first week (74% of the Swiss infants <27 completed weeks), and 62% were alive after 28 days (respective 63% in Switzerland). The mortality rate amounted to 42% (respective 44% in Switzerland).

Rijken [39] could show as part of the Leiden Follow-up Project on Prematurity (LFUPP) that very preterm infants of two Dutch health regions had a reduced length, weight and a similar head circumference at two years corrected age[28] compared to the Dutch growth charts. Further, growth retardation was associated with an abnormal neurologic examination. He argued that the postnatal application of dexamethasone may be a significant contributing factor for the latter. For the Swiss very preterm infants, Bucher [17] could show a poorer neurological outcome at two years corrected age as well and less children had an overall fair outcome, defined as survivor without serious neonatal complications or abnormal neurological findings.

[28] The corrected age should be used for developmental evaluations of infants with <40 completed gestational weeks throughout the first 2-3 years of life. Age correction may reduce parental anxiety and decrease referral services [72].

Table 20: Comparison between Switzerland and other countries with international studies that used the gestational age as inclusion criteria.

Year	Switzerland 1996	Netherland[1] 1996-1997	Sweden[2] 1992-98	Belgium[3] 1999-2000	New Zealand[4] 1998-1999	Australia, New Zealand[5] 1996
Database inclusion criteria	< 32 completed weeks	< 32 completed weeks	singletons <32 completed weeks	NICU < 27 completed weeks	< 32 completed weeks	< 32 completed weeks
No. of infants	573	266	2253	525	3368	2964
Male	53.4%	55.3%	54.9%	53.8%	53.8%	
Multiple birth	23.0%	31.6%[b]		35.3%	28.2%[a]	25.8%
Caesarean section	71.2%	39.8%[c]	64.1%[b]	23.6%[c]		55.7%[c]
SGA	9.4%	12.4%	29.9%[c]			
Congenital malformation	7.5%	5.3%		6.6%	5.0%[a]	
PDA	17.1%	26.3%[b]		43.0%		
Sepsis	9.6%	27.1%[c]		14.9%	26.2%[c]	
NEC	3.8%	9.4%[b]			3.3%	
RDS (grade 1-4)	80.8%	58.6%[c]		86.1%		
CLD	32.9%					33.2%
BDP	14.4%	18.4%[a]			12.8%	16.9%[a]
ROP stage 3-4	2.2%				1.8%	6.8%[c]
IVH grade 1-4	23.2%	24.8%		46.2%		
IVH grade 3-4	7.3%	7.5%		23.1%	4.8%[a]	7.0%
Cystic PVL	3.0%			6.9%	12.6%[a]	
LOS of survivors (days)	67.3	44		96		
Early mortality	8.4%	55.2%		29.4%		
Late mortality	3.2%	37.9%		11.7%		
Mortality >28d	1.2%	6.9%				
Neonatal mortality	11.3%	10.9%		46.2%		
Mortality rate	12.4%		11.9%	42.2%	9.0%[a]	
Steroid	64.2%	68.4%		45.9%	63.7%[b]	76.4%[a]
Surfactant	30.0%	42.1%[b]		77.9%	39.5%[b]	56.3%[c]
Mechanical ventilation	52.0%	74.8%		93.4%	92.2%[c]	
CPAP treatment	48.2%					59.9%[c]
Major surgery	5.1%				7.2%[c]	

Lit:
1: Stoelhorst: Leiden Follow-Up Project
2: Johansson
3: Vanhaesebrouck. EPIBEL Study
4: Cust, Darlow. Outcomes for high risk 98-99
5: Donoghue

Significant levels: Switzerland versus other country (exclusive Belgium)
a:<0.05
b:<0.01
c:<0.0001

4.6.4 Comparison by birth weight

In the last decades it was more common to analyse very low birth weight infants (VLBW) instead of using the gestational age as inclusion criteria. When it became easier to assess the age of newborns, more and more research was done on the basis of the gestational age. Nevertheless up to now, more international publications with the birth weight as inclusion criteria are available.

Like the publication based on the gestational age, the rate of females (about 50%) corresponded between the countries, less Swiss multiple births were observed than in most of the other countries and the C-section was done more frequently in Switzerland than abroad (Table 21).
The incidence of PDA, proven NEC, proven sepsis, BPD and ROP was significantly lower in Switzerland than in the other publications. The reason is most likely to find in the different definitions in the countries. The frequency of infants with a RDS was similar in Switzerland than in Finland in both years, however significantly higher in Switzerland than in Portugal, USA or the average than the 39 countries[29] that participated for nine years in the Vermont Network. The incidence of an intracranial haemorrhage grade 3-4 was similar in Switzerland (about 7%) as in the Vermont Network – although an increase from 1996 to 1999 was observed in the Vermont Network opposite to a decrease in Switzerland - or Canada, however significantly lower than in Finland in both years (about 16%) or in the USA (12%).
The mortality rate didn't differ significantly between the countries. The increase in mortality between 1996 and 2000 that could be observed in Switzerland can also be found in the Vermont Network. The early and therefore the neonatal mortality rate were significantly lower in Switzerland than in Finland. No reason was found.
Antenatal steroids were given at the same level in most of the examined countries with increasing frequency between 1996 (about 60%) and 2000 (75%). Only in the USA, antenatal steroids were given significantly more often (79%) in 2000. Surfactant was given significantly less frequently in Switzerland (less than 30%) than abroad (above 50%). The same is true for the mechanical ventilation – about 45% in Switzerland compared to above 60% in the other countries, although a decrease over the years was observed in all mentioned publications. The rate of CPAP treatments increased in all countries between 1996 and 2000 with a significant lower frequency in Portugal (only 40% in 2000 compared to 60% in Switzerland respectively the Vermont Network).

The Epipage study[30] included very preterm infants born in nine regions of France in 1997 [27]. The survival rate amounted to 67% of all births inclusive stillbirth – 85% of the Swiss very preterm infants born in 1996 inclusive deaths in delivery room - and 85% of live births – 88% in Switzerland (1996). For live births, the survival was lower for SGA infants, multiple births and boys – the same result in Switzerland for SGA infants and males; however the Swiss multiple births had a better survival rate in 1996 than singletons.

A population-based study of Swedish very preterm infants born in the period 1992-98 [26] revealed that infants with 24-27 completed weeks had a significant higher risk of death when they were born in general hospitals than in university hospitals. The mortality rate of the Swedish children with 24 completed weeks amounted to 56% - compared to 75% of the Swiss liveborns in perinatal centres in 1996 - and decreased to 5% for the ones with 31 completed weeks – compared to 3% in Switzerland. In Sweden, LGA and SGA infants had a significant higher risk of death than AGA ones. Likewise the males had a significant higher risk than females. The lethal risk didn't differ between the different modes of delivery. A contradictory result was given in Switzerland: the risk didn't differ significantly between SGA respective LGA infants and AGA ones. Also the gender hadn't an effect on the mortality. However the children born by C-section had a significant lower lethal risk than vaginal delivered ones.

[29] Switzerland wasn't included.
[30] The Epipage study examined the behavioural outcome at 3 years of age as well [43]. Very preterm infants had more likely behavioural difficulties than term-born children and associated factors were major neonatal cerebral lesions, hospitalisation within the last year, poor health and psychomotor delay. Other risk factors were a high birth order and sociodemographic factors - e.g. .young maternal age, a mother's low educational level.

Fanaroff et al [70] couldn't find any significant increases in survivors without neonatal - defined by BPD, IVH and NEC - and long-term morbidity among VLBW infants of 16 US centres between 1997 and 2002. The use of steroids declined over the period.

Table 21: Comparison between Switzerland and other countries with international studies that used the birth weight as inclusion criteria

	Switzerland		Portugal [15]		Finland [23, 79]		Vermont Network [14][1]		Canada [8]	USA[70]
Year	1996	2000	1996	2000	1996-1997	1999-2000	1996	1999	1996-1997	1997-2002
Database inclusion criteria	< 1500g		< 1500g		< 1000g		501-1500g		< 1500g	501-1500g
No. of infants	549	598	830	1042	351	339	3645	3767	3779	18153
Mean BW	1101	1082			750	738	1042	1032		
Mean GA	29.6	29.1			26.4	26.3	28.3	28.2		
Female	50.0%	53.3%			50.7%	50%	49.1%	46.8%[c]		26%
Multiple birth	22.8%	28.0%	22%	29%	29.1%[b]	25%	28.4%[b]	29.5%[c]		
Cesarean section	76.0%	81.3%	54%[c]	65%[c]	52.7%[c]	54%[c]	59.5%[c]	61.5%[c]		58%[c]
Inborn	87.5%	88.4%					50.9%[c]	83.0%[c]		
SGA	27.2%	23.7%			34.0%[a]	35%[b]	20.4%[b]	19.2%[b]		21%
PDA	16.9%	21.0%			46%[c]					29%[c]
Sepsis	10.3%	13.9%	34%[c]	29%[c]	22%[c]	31%[c]				
NEC	3.8%	3.8%	12%[c]	10%[c]	9%[b]		7.3%[b]	7.4%[b]	7%[b]	7%[b]
ROP stage 1-4	12.0%	11.9%	22%[c]	19%[b]						
ROP stage 3-4	2.1%	0.7%			9%[c]				11%[c]	
RDS	75.7%	79.2%	57%[c]	60%[c]	76%	83%	66.0%[c]	70.7%[c]		44%[c]
CLD										25%
BPD	16.6%	12.1%	23%[b]	23%[c]	39%[c]	39%[c]				22%[c]
IVH grades 1-4	21.9%	26.2%	32%[c]	20%[b]	27%	37%[b]	25.0%	24.6%	32%[c]	27%
IVH grades 3-4	7.4%	7.2%			16%[b]	17%[c]	6.9%	8.2%	10%	12%[b]
Early mortality	8.7%	10.0%			21%[c]					
Late mortality	3.1%	4.6%			3.0%					
Neonatal mortality	11.6%	14.1%			38%[c]					
Mortality rate	13.1%	16.5%					14.0%	15.1%	13%	15%
Antenatal steroids	60.3%	74.5%	54%[c]	74%	66%		66.9%	75.0%		79%[c]
Surfactant	27.8%	32.5%	50%[c]	48%[c]			58.8%[c]	63.4%[c]		58%[c]
Mech. ventilation	49.0%	43.3%	67%[c]	61%[c]			76.6%[c]	76.2%[c]		
CPAP treatment	45.4%	64.3%	19%[c]	40%[c]			52.1%[b]	62.5%		

1: 39 perincatal centres, that participated for 9 years

Significant levels: Switzerland versus other country
a:<0.05
b:<0.01
c:<0.0001

4.7 Mathematical models

4.7.1 Linear model of the gestational age at dismission

A gestational age at dismission could only be calculated for 1458 survivors delivered to the perinatal centres. The rest were excluded for the linear regression with the gestational age at birth as independent variable and the gestational age at dismission as dependent variable. The

linear dependency was significantly with a low R squared (F=137.44, p<0.0001, adjusted R^2=0.086, Durbin Watson 1.795). The linear equation was

GA_dismission(weeks)= 54.555 – 0.537 * GA_birth(weeks)

with a 95% CI (t=40.48, p<0.0001) 51.911-57.199 for the constant variable and a 95% CI (t=11.73, p<0.0001) –0.626 to -0.447 for the independent variable. The younger a child at birth was, the older it was expected when it was dismissed to home.

A linear model of the gestational age at dismission using the variables that were known at birth – defined as birth and the first 24 hours of life. The gestational age at birth, the birth weight, the head circumference, the gender, the information if singleton or multiple birth, the mode of delivery, the pH of the umbilical artery, all three APGAR scores, the major congenital malformation and respiratory distress syndrome were entered stepwise. 853 survivors were used for the analysis. The model was significant with a better, but still poor R squared (F=35.88, p<0.0001, adjusted R^2=0.170, Durbin Watson 1.768). The significant variables supporting the model were the birth weight, the head circumference, the information about multiple birth, the APGAR score after 5 minutes and the congenital malformation:

	Coefficients	t-value	Significance	95% Confidence Interval for Coefficients
(Constant)	48.454	31.89	2.6E-147	(45.472, 51.436)
Birth weight	-0.002	-3.41	6.7E-04	(-0.003, -0.001)
Head circumference	-0.019	-2.67	7.7E-03	(-0.033, -0.005)
Multiple birth	-0.691	-3.02	2.6E-03	(-1.141, -0.242
APGAR after 5 min	-0.285	-4.12	4.1E-05	(-0.420, -0.149)
Cong. Malformation	3.995	6.42	2.3E-10	(2.774, 5.217)

An extension of this model included all others as well inclusive the therapies. The linear regression took 741 survivors into consideration. The quality of the model was better (F=107.13, p<0.0001, adjusted R^2=0.276, Durbin Watson 2.899). The significant variables with a positive coefficient were the morbidities - the major congenital malformation, the proven sepsis, the BPD, the intracranial haemorrhage grade 3-4 - and therapies - the mechanical ventilation and the major surgery. The significant ones with a negative coefficient were the demographics – the head circumference, the information about multiple birth and the APGAR score after 1 minute.
The more variables supported the model the better the prediction quality was. Nevertheless the adjusted R squared wasn't sufficient high. The gestational age didn't support any of the models. The APGAR score was significantly in all models however it changed which one was considered.

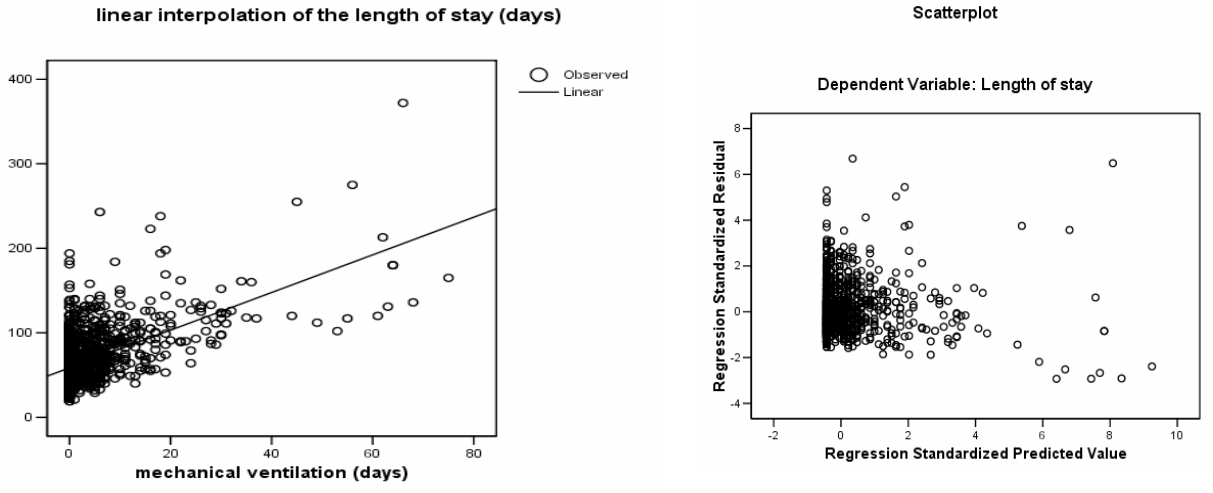
4.7.2 Linear model of the length of stay

A linear regression (Figure 41) showed a significant positive linear dependency between the length of stay - 1458 survivors delivered to the perinatal centres - as dependent variable and the duration of mechanical ventilation as independent variable (F=669.20, p<0.0001, adjusted R^2=0.314, Durbin-Watson 1.757). The expected linear equation was

LOS(days)= 58.429 + 2.236 * mech.ventilation(days)

with a 95% CI 57.000-59.858 (t=80.20, p<0.0001) for the constant variable and a 95% CI 2.066-2.405 (t=25.87, p<0.0001) for the independent variable. Due to this model, the expected length of stay of an infant with no mechanical ventilation is 58.4 days.

Figure 41: The linear regression between the duration of mechanical ventilation and the length of stay of the survivors delivered to the perinatal centres.



A linear regression using only the 619 mechanical ventilated survivors with a known length of stay showed a significant positive linear dependency as well with a little better prediction quality (F=293.68, p<0.0001, adjusted R^2=0.321, Durbin-Watson 1.774). The expected linear equation was

$$LOS(days)= 64.553 + 1.951 * mech.ventilation(days)$$

with a 95% CI 61.661-67.445 (t=43.84, p<0.0001) for the constant variable and a 95% CI 1.727-2.174 (t=17.14, p<0.0001) for the independent variable. Due to this model, a child was expected to stay almost 2.0 days in hospital for each day of mechanical ventilation.

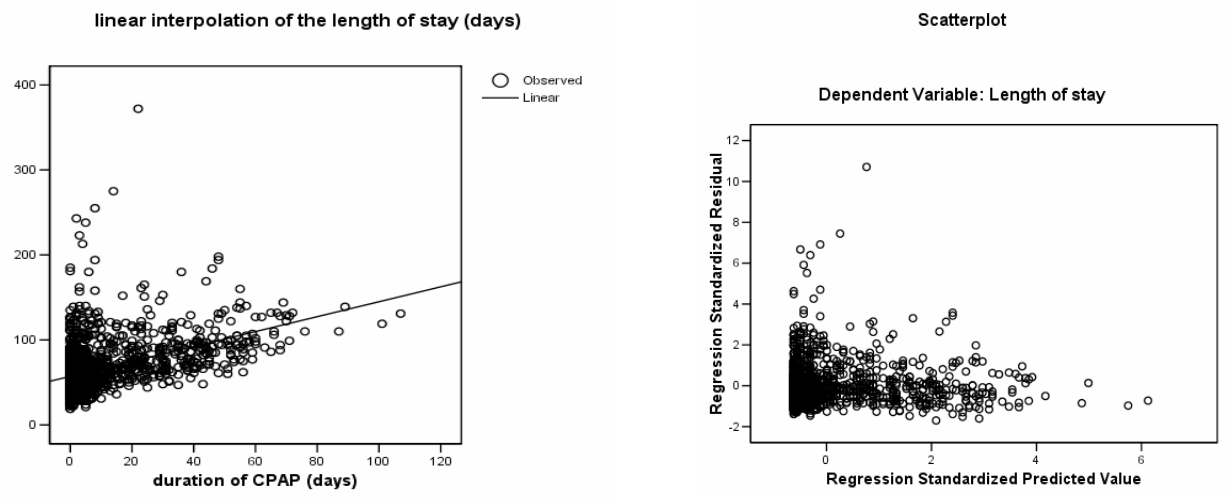
A linear regression (Figure 42) showed a significant positive linear dependency between the length of stay as dependent variable and the duration of CPAP treatment as independent variable (F=370.64, p<0.0001, adjusted R^2=0.202, Durbin-Watson 1.761). The expected linear equation - 1458 survivors delivered to the perinatal centres were considered[31] - was

$$LOS(days)= 57.133 + 0.878 * CPAP(days)$$

with a 95% CI 55.461-58.805 (t=67.04, p<0.0001) for the constant variable and a 95% CI 0.789-0.967 (t=19.25, p<0.0001) for the independent variable. Due to this model, the expected length of stay of an infant with no CPAP treatment was 57.1 days, circa 1.5 days shorter –although not significant different - than the value calculated with the linear regression model of LOS with the duration of mechanical ventilation.

[31] A linear regression using only the 1001 CPAP ventilated survivors had a slightly poorer quality (F=218.03, p<0.0001, adjusted R^2=0.178, Durbin-Watson 1.719). The expected linear equation was LOS(days)= 59.731 + 0.804 * CPAP(days) with a 95% CI 57.320-62.142 (t=48.62, p<0.0001) for the constant variable and a 95% CI 0.697-0.911 (t=14.77, p<0.0001) for the independent variable.

Figure 42: The linear regression between the duration of CPAP treatment and the length of stay of the survivors delivered to the perinatal centres.



The prediction quality of a linear model[32] using the 516 survivors with only CPAP treatment and no mechanical ventilation was worse than the model using mechanical ventilation, however better than the one using CPAP treatment ($F=181.61$, $p<0.0001$, adjusted $R^2=0.260$, Durbin-Watson 1.833).

A stepwise linear regression of the length of stay using the 1458 survivors[33] and the duration of CPAP treatment and mechanical ventilation delivered a similar significant result ($F=620.41$, $p<0.0001$, adjusted $R^2=0.460$, Durbin-Watson 1.717) as the linear regression with each of the independent variables:

	Coefficients	t-value	Significance	95% Confidence Interval for Coefficients
(Constant)	51.661	70.61	0	(50.225, 53.096)
days of ventilation	2.038	26.34	2.36E-125	(1.887, 2.190)
days of CPAP	0.749	19.80	1.98E-77	(0.675, 0.824)

A linear regression using all 1610 survivors showed a significant positive linear dependency between the length of stay as dependent variable and the duration of respiratory support - CPAP treatment and/or mechanical ventilation - as independent variable ($F=911.16$, $p<0.0001$, adjusted $R^2=0.384$, Durbin-Watson 1.678). The expected linear equation (Figure 43) was

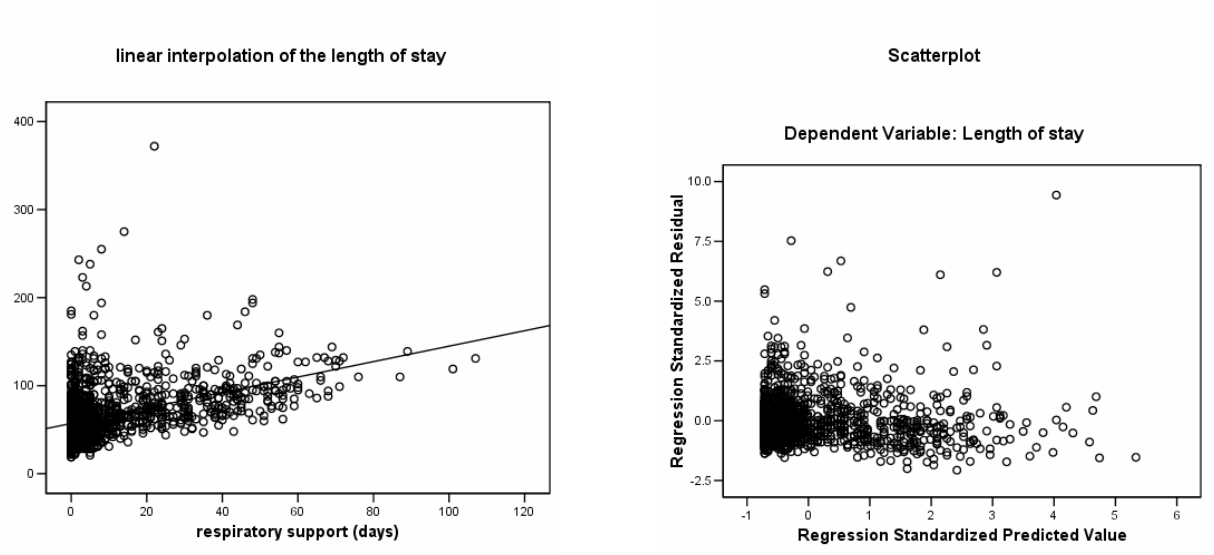
$$LOS(days)= 52.155 + 1.035 * respiratory\ support(days)$$

with a 95% CI 50.625-53.685 ($t=66.87$, $p<0.001$) for the constant variable and a 95% CI 0.968-1.102 ($t=30.19$, $p<0.0001$) for the independent variable. Due to this model, a child was expected to stay 1 day more than 52 days for each day of respiratory support.

[32] The expected linear equation is LOS(days)= 51.021 + 0.768 * CPAP(days) with a 95% CI 48.897-53.144 ($t=47.21$, $p<0.0001$) for the constant variable and a 95% CI 0.656-0.880 ($t=13.48$, $p<0.0001$) for the independent variable. A child is expected to stay significantly shorter in a hospital using this model than with the model calculated with all survivors who received CPAP with or without mechanical ventilation.

[33] Using only the 1135 infants who received either a CPAP or a mechanical ventilation, the model was slightly worse ($F=466.99$, $p<0.0001$, adjusted $R^2=0.451$, Durbin-Watson 1.748).

Figure 43: Duration of respiratory support per LOS of the survivors.



A linear regression using only the 1135 survivors with a respiratory support showed only a little different result (F=645.92, p<0.0001, adjusted R^2=0.363, Durbin-Watson 1.645). The expected linear equation was

$$\text{LOS(days)} = 53.778 + 0.993 * \text{respiratory support(days)}$$

with a 95% CI 51.800-55.755 (t=53.36, p<0.0001) for the constant variable and a 95% CI 0.917-1.070 (t=25.41, p<0.0001) for the independent variable.

4.7.3 Factor model

The factor models were calculated only for the survivors. A first model used the variables gestational age, birth weight, head circumference, pH-value of the umbilical artery, birth location, gender, mode of delivery, multiple birth and all three APGAR scores. 971 data records were available. A closer examination of the correlation matrix[34] (Table 22) - the determinant amounted to 0.021 and was therefore non-singular - showed an obviously high and significant correlation between the gestational age, the birth weight and the head circumference. The three APGAR scores had a high and significant correlation as well. A significant correlation could be found between the pH-value of the umbilical artery and all three APGAR scores and the mode of delivery. The gender and the birth location had hardly significant correlations. The information of multiple birth was significantly for most of the other variables.

[34] The Kaiser-Mever-Olkin measure of sampling adequacy (MSA) amounted to 0.71 for the correlation matrix. The criteria of Dziuban-Shirkey was less than 0.25 and indicated that the correlation matrix couldn't actually be used for the factor analysis.

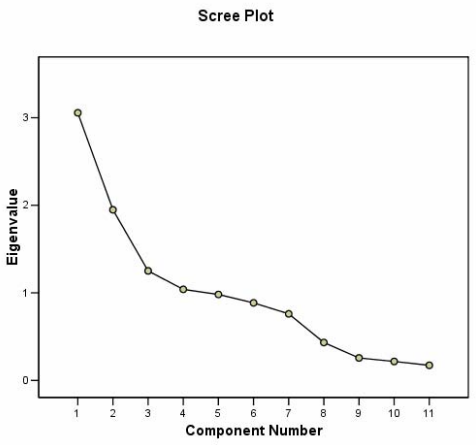
Table 22: Correlation matrix of the variables in the first factor model.

Correlation matrix	GA	BW	Head circumf.	pH	APGAR 1 min	APGAR 5 min	APGAR 10 min	Birth loc.	Gender	Mode of delivery
Birth weight	0.74[d]									
Head circumf.	0.72[d]	0.80[d]								
Umb. artery pH	0.00	0.09[b]	0.08							
APGAR 1 min	0.25[d]	0.21[d]	0.18[d]	0.27[d]						
APGAR 5 min	0.23[d]	0.13[d]	0.13[d]	0.21[d]	0.66[d]					
APGAR 10 min	0.23[d]	0.13[d]	0.10[c]	0.17[d]	0.55[d]	0.77[d]				
Birth location	0.03	0.05	0.05	-0.07[a]	0.04	-0.01	-0.05			
Gender	-0.01	0.10[c]	0.09[b]	0.02	0.08[b]	0.08	0.06[a]	0.03		
Mode of delivery	0.02	0.19[d]	0.05	0.14[d]	0.02	0.01	0.01	0.03	0.03	
Multiple birth	-0.13[d]	-0.07[a]	-0.10[b]	0.02	-0.13[d]	-0.06[a]	-0.06[a]	0.03	-0.01	0.17[d]

[a]: p< 0.05
[b]: p< 0.01
[c]: p< 0.001
[d]: p< 0.0001

Table 23: A factor model using the principal component analysis (variables as in Table 22)

Component	Initial Eigenvalues		
	Total	% of Variance	Cumulative %
1	3.06	27.78	27.78
2	1.95	17.71	45.49
3	1.25	11.37	56.86
4	1.04	9.45	66.32
5	0.98	8.92	75.24
6	0.89	8.05	83.29
7	0.76	6.91	90.20
8	0.43	3.94	94.13
9	0.26	2.33	96.47
10	0.22	1.97	98.43
11	0.17	1.57	100.00

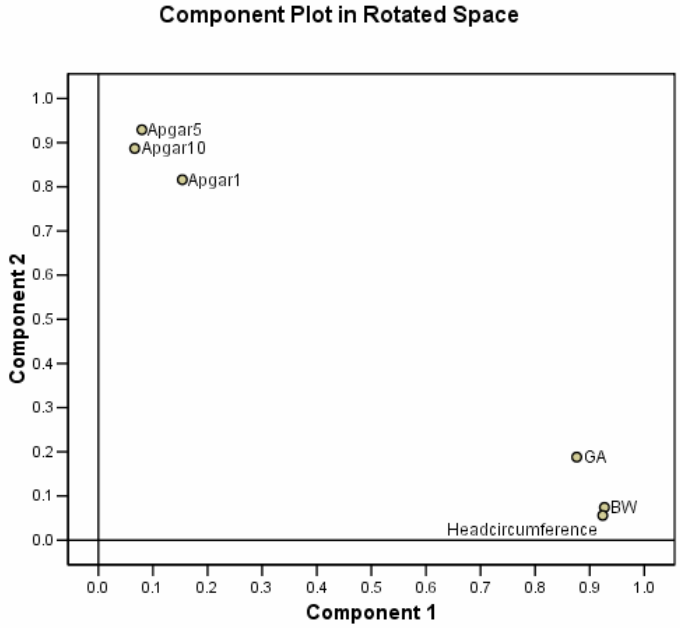


After closer examination of the correlation matrix obviously a first factor or principal component embraced the three variables gestational age, birth weight and head circumference. A second factor or principal component embraced all three APGAR scores. All other variables couldn't be grouped together. Seven factors or principal components were needed to explain at least 90% of the variance (Table 23). The component score coefficient matrix (Table 24) showed – the factor score coefficient matrix looks similar – that the first component contained the information about gestational age, birth weight and head circumference, the second component contained the information of the three APGAR scores, the third component was more or less the mode of delivery, the fourth one was the pH-value of the umbilical artery, the fifth one was the gender, the sixth one was the birth location and the seventh component was the multiple birth. An eighth component would contain most of the information of the gestational age, a ninth one would mainly be the same as the APGAR score after 1 minute.
A graphical representation (Figure 44) of the first two components showed the grouping of the variables gestational age, birth weight, head circumference, APGAR scores.

Table 24: Coefficient Matrix of the 7 principal components of the factor model.

Component Score Coefficient Matrix	Component						
	1	2	3	4	5	6	7
Gestational age	**0.360**	0.027	-0.068	-0.117	-0.114	-0.027	0.016
Birth weight	**0.372**	-0.060	0.085	0.027	0.037	-0.011	0.026
Head circumference	**0.388**	-0.079	-0.095	0.064	0.035	-0.006	0.043
Umbilical artery pH	-0.010	-0.074	-0.073	**0.995**	-0.017	0.015	0.005
APGAR after 1 min	-0.020	**0.318**	-0.014	0.115	-0.005	0.101	-0.076
APGAR after 5 min	-0.051	**0.422**	0.005	-0.092	-0.004	-0.007	0.053
APGAR after 10 min	-0.048	**0.420**	0.025	-0.166	-0.026	-0.070	0.069
Birth location	-0.020	0.007	-0.011	0.018	-0.016	**0.992**	-0.004
Gender	-0.018	-0.015	-0.017	-0.018	**0.991**	-0.017	0.000
Mode of delivery	-0.038	0.009	**1.008**	-0.077	-0.019	-0.012	-0.095
Multiple birth	0.039	0.027	-0.098	0.003	-0.001	-0.004	**1.011**

Figure 44: The first two components of the factor model as in Table 24.



To identify possible variables supporting a discriminant model, we analysed a factor model using all variables that are mentioned in the previous chapters. The analysis was done separately for the survivors - 836 data records - and the deaths - 81 data records, as well for the total population. The statistics of the variables showed differences between the groups (cf. Table 25), and it was interesting to see if it had an effect on the number of independent principal components or factors[35].

[35] The result of the method of principal axis factoring isn't provided because of the difficult interpretation of the factors.

Table 25: Statistics of variables used for the factor analysis.

	Survivor		Deaths		Population	
	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation
Gestational age	29.44	1.90	26.91	2.05	29.22	2.04
Birth weight	1271.62	356.76	863.09	370.08	1235.53	376.09
Head circumference	272.21	25.92	245.86	33.28	269.89	27.66
Umbilical artery pH	7.27	0.09	7.23	0.12	7.27	0.09
APGAR after 1 minute	6.05	2.28	3.88	2.30	5.86	2.36
APGAR after 5 minutes	8.04	1.51	6.52	1.95	7.91	1.61
APGAR after 10 minutes	8.69	1.16	7.88	1.40	8.62	1.20
Birth location	1.08	0.27	1.09	0.28	1.08	0.27
Gender	1.53	0.50	1.60	0.49	1.53	0.50
Mode of delivery	0.22	0.42	0.22	0.42	0.22	0.42
Multiple birth	0.70	0.46	0.77	0.43	0.71	0.45
SHC	0.07	0.25	0.22	0.42	0.08	0.27
SGA	0.10	0.30	0.26	0.44	0.11	0.32
Congenital malformation	0.03	0.17	0.09	0.28	0.03	0.18
PDA	0.17	0.38	0.38	0.49	0.19	0.39
Intracran. haemorrhage grade 3-4	0.03	0.18	0.21	0.41	0.05	0.21
PVL	0.02	0.14	0.05	0.22	0.02	0.15
NEC	0.02	0.15	0.15	0.36	0.03	0.18
Sepsis	0.11	0.32	0.17	0.38	0.12	0.32
CLD	0.28	0.45	0.12	0.33	0.26	0.44
BPD	0.12	0.32	0.04	0.19	0.11	0.31
RDS	0.83	0.37	0.95	0.22	0.84	0.37
Mechanical ventilation	0.37	0.48	0.85	0.36	0.41	0.49
CPAP treatment	0.77	0.42	0.46	0.50	0.74	0.44
Surfactant	0.28	0.45	0.63	0.49	0.31	0.46
Antenatal steroids	0.73	0.44	0.62	0.49	0.72	0.45
Surgery	0.04	0.21	0.21	0.41	0.06	0.24

Birth location (1=Inborn, 2=Outborn), Gender (1=Female, 2=Male), Mode of delivery (0=C-section, 1=Vaginal delivery), Multiple birth (0=Multiple birth, 1=Single birth), SHC anad SGA (0=no, 1=yes), Congenital malformation (0=none or minor, 1=major), other morbidities (0=no, 1=yes), Surgery (0=none or minor, 1=major), other therapies (0=no, 1=yes)

The Kaiser-Mever-Olkin measure of sampling adequacy (MSA) amounted to 0.75 for the subgroup of the survivors. The criterion of Dziuban and Shirkey was 0.07 and indicated again that the correlation matrix couldn't be used for the factor analysis. The principal component analysis showed that each of the first two components contained the information of more than one variable. The first one represented the dimension of the gestational age, the birth weight and the head circumference, the second one the dimension of the APGAR score after 5 and 10 minutes. All other variables were represented by one principal component. Therefore 24 components were needed to describe the space of the 27 variables, and these described 98% of the total variance (Table 26).

The correlation matrix for the deaths had a MSA of 0.58 and the criteria of Dziban-Shirkey amounted to 0.17. Both criteria didn't fulfil the criteria for usefulness of the correlation matrix. Each of the first three principal components represented the dimension of more than one variable. The first one had the same interpretation like the one for the survivors. The information of the SGA and SHC infants were aggregated in the second component and the third one represented again the APGAR score after 5 and 10 minutes. All other components

could be interpreted as one of the variables. Therefore 23 components described the dimensions of all variables and 98% of their variance (Table 24).

Table 26: Initial eigenvalues of the factor analysis for the three subgroups.

	Survivor			Death			Population		
Component	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	4.79	17.74	17.74	3.62	13.40	13.40	4.81	17.80	17.80
2	2.45	9.07	26.81	3.29	12.19	25.60	2.35	8.69	26.48
3	1.64	6.09	32.90	2.54	9.42	35.02	1.77	6.56	33.04
4	1.45	5.37	38.27	2.20	8.14	43.16	1.44	5.35	38.39
5	1.34	4.96	43.23	1.80	6.66	49.81	1.34	4.98	43.37
6	1.31	4.85	48.07	1.42	5.25	55.06	1.29	4.78	48.15
7	1.24	4.60	52.67	1.33	4.91	59.97	1.23	4.55	52.70
8	1.17	4.32	57.00	1.29	4.77	64.73	1.19	4.42	57.12
9	1.14	4.21	61.21	1.12	4.13	68.87	1.12	4.14	61.26
10	1.05	3.90	65.11	1.07	3.95	72.82	1.05	3.89	65.15
11	0.96	3.57	68.68	1.03	3.81	76.63	1.02	3.77	68.91
12	0.91	3.38	72.06	0.88	3.27	79.90	0.92	3.42	72.34
13	0.87	3.21	75.27	0.73	2.70	82.59	0.87	3.21	75.55
14	0.84	3.11	78.38	0.69	2.54	85.13	0.84	3.10	78.64
15	0.76	2.83	81.21	0.59	2.20	87.34	0.76	2.82	81.46
16	0.75	2.79	83.99	0.52	1.93	89.27	0.71	2.63	84.09
17	0.66	2.45	86.45	0.47	1.75	91.02	0.71	2.62	86.72
18	0.62	2.31	88.76	0.41	1.53	92.55	0.64	2.39	89.10
19	0.60	2.22	90.98	0.40	1.48	94.03	0.56	2.06	91.17
20	0.44	1.63	92.61	0.36	1.32	95.35	0.45	1.67	92.83
21	0.43	1.59	94.20	0.31	1.13	96.48	0.41	1.53	94.36
22	0.42	1.55	95.75	0.24	0.90	97.38	0.40	1.48	95.84
23	0.34	1.24	97.00	0.21	0.79	98.16	0.34	1.27	97.11
24	0.28	1.02	98.02	0.17	0.61	98.78	0.28	1.04	98.15
25	0.21	0.78	98.80	0.15	0.55	99.33	0.20	0.74	98.89
26	0.19	0.71	99.51	0.10	0.36	99.69	0.18	0.66	99.55
27	0.13	0.49	100.00	0.08	0.31	100.00	0.12	0.45	100.00

Using the total population, the model was similar to the one of the survivors as expected. The MSA of the correlation matrix amounted to 0.75 and the criteria of Dziuban-Shirkey to 0.07. The interpretation of the principal components was the same as for the survivors and therefore 24 components were needed to describe 98% of the variance of the variables.

The result indicated that almost all variables had to be used for a prognosis model. Only the gestational age, the birth weight, the head circumference, the SGA infants, the SHC ones and all three APGAR scores had some redundant information. Therefore it might be useful to calculate a separate discriminant model that used only the gestational age, the SGA infants, the SHC ones, the APGAR score after 1 minute and after 5 minutes.

4.7.4 Discriminant model for survivor/death

First, we used the demographic variables in order to discriminate the deaths from the survivors[36]. Then another models was calculated with all variables inclusive the morbidity and the therapeutic variables.

Table 27: Statistic of variables used in discriminant analysis.

	Survivor		Death		Population	
	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation
Gestational age	29.37	1.91	26.91	1.97	29.12	2.06
Birth weight	1263.53	357.98	886.32	349.32	1225.15	374.74
Head circumference	271.55	26.02	246.72	30.55	269.02	27.55
Umbilical artery pH	7.27	0.09	7.24	0.12	7.27	0.10
APGAR after 1 minute	5.98	2.32	3.82	2.32	5.76	2.41
APGAR after 5 minutes	8.01	1.53	6.34	2.06	7.84	1.67
APGAR after 10 minutes	8.66	1.19	7.70	1.58	8.56	1.27
Birth location	1.07	0.26	1.06	0.25	1.07	0.26
Gender	1.51	0.50	1.63	0.49	1.53	0.50
Mode of delivery	0.23	0.42	0.26	0.44	0.24	0.43
Multiple birth	0.70	0.46	0.73	0.45	0.70	0.46

Birth location (1=Inborn, 2=Outborn), Gender (1=Female, 2=Male), Mode of delivery (0=C-section, 1=Vaginal delivery), Multiple birth (0=Multiple birth, 1=Single birth)

Table 28: The standardized canonical discriminant function coefficients.

	Standardized Canonical Discriminant Function Coefficients
Gestational age	0.549
Birth weight	0.310
Head circumference	-0.099
Umbilical artery pH	0.028
APGAR after 1 minute	0.140
APGAR after 5 minutes	0.552
APGAR after 10 minutes	-0.143
Birth location	-0.027
Gender	-0.190
Mode of delivery	-0.119
Multiple birth	0.092

A first model discriminated the survivors from the deaths using the variables gestational age, birth weight, head circumference, pH-value of the umbilical artery, birth location, gender, mode of delivery, multiple birth and all three APGAR scores. 1081 data records were used, 971 survivors and 110 deaths. As already mentioned, the group statistics (Table 27) differed for the gestational age, birth weight, head circumference and all three APGAR scores. The covariance matrix of the two groups was significantly different (Box M-statistic 153.85, $p<0.0001$). The Wilks'Lambda (0.81) of the discriminant function indicate a low discriminatory ability of the function, however it is significantly ($p<0.0001$). The gestational age and the APGAR score after 5 minutes were the variables with the biggest discriminatory power (Table 28). The pH-value of the umbilical artery and the birth location were the ones

[36] Ambalavanan [30] used a multiple logistic regression and a neural network model to predict death using the data of infants below 1000g born in the period 1998-2003. They argued that the ability to predict death is significant better at 5 minutes of age than at or before birth, also the prediction doesn't improve with increasing age.

with the smallest discriminatory power. 78% of the original data were classified (Table 29) correctly with the discriminant function and it showed a sensitivity of 77.3% (95% CI 74.7-79.8%) and specificity of 78.1% (95% CI 75.5-80.6%). The positive predictive value (PPV) amounted to 28.5% (95% CI 25.8-31.3%), the negative predictive value (NPV) was 96.8% (95% CI 95.7-97.9%). Instead using the observed group sizes instead equal prior probabilities as prior probabilities, 91% of the original data were classified correctly, however the sensitivity and specificity decreased.

Table 29: Classification result of the discriminant function as in Table with the original data and the equal (observed group size) prior probability.

	Survivor/Death	Predicted Group Membership		Total
		Survivor	Death	
Count	Survivor	758 (946)	213 (25)	971
	Death	25 (71)	85 (39)	110
%	Survivor	78.1 (97.4)	21.9 (2.6)	100.0
	Death	22.7 (64.5)	77.3 (35.5)	100.0

Applying the result from the previous chapter and using the variables "representing" the dimension of all variables, 920 data records - 836 survivors and 84 deaths – were used. The Box's M of 1224.8 indicates a significant difference of the covariance matrix between the two groups ($p<0.0001$). The Wilks'Lambda amounted to 0.58 ($p<0.0001$) and was a little less than in the above model of all variables. The discriminatory power of the variables didn't change much compared to the last model: the most important ones were again the gestational age, followed by CLD and CPAP treatment; the least important ones were mode of delivery, multiple birth, PVL and surfactant (Table 30). The amount of correct specified data (Table 31) was 92.3% (95% with observed group sizes as prior probabilities) with a bit better sensitivity of 84.5% (95% CI 82.1-86.9%), specificity[37] of 93.1% (95% CI 91.4%-94.7%), a PPV of 55.0% (95% CI 51.8%-58.3%) and a NPV of 98.4% (95% CI 97.5%-99.2%) (cf Table 31).

Table 30: The standardized canonical discriminant function coefficients.

Function coefficients	Coefficient	Function coefficients	Coefficient
Gestational age	0.690	Intracran. haemorrhage grade 3-4	-0.261
Umbilical artery pH	0.061	PVL	-0.052
APGAR after 1 minute	0.165	NEC	-0.180
APGAR after 5 minutes	0.115	Sepsis	0.075
Birth location	-0.086	CLD	0.606
Gender	-0.091	BPD	0.076
Mode of delivery	0.013	RDS	-0.287
Multiple birth	0.046	Mechanical ventilation	-0.167
SGA	-0.157	CPAP treatment	0.539
SHC	-0.197	Surfactant	-0.028
Congenital malformation	-0.201	Antenatal steroids	-0.085
PDA	-0.115	Surgery	-0.218

[37] Using all variables , the Wilks'Lambda didn't change and the amount of correct specified data was 92.6% with a sensitivity of 85.2%, a specifity of 93.3%, a PPV of 55.2% and a NPV of 98.5%.

Table 31: Classification result of the discriminant function with the original data and the equal (observed group size) prior probability.

	Survivor/Death	Predicted Group Membership		Total
		Survivor	Death	
Count	Survivor	778 (815)	58 (21)	836
	Death	13 (27)	71 (57)	84
%	Survivor	93.1 (97.5)	6.9 (2.5)	100.0
	Death	15.5 (32.1)	84.5 (67.9)	100.0

The more variables were used, the better discriminatory power of the model and therefore the more infants were specified correctly.

4.7.5 Discriminant model for the outcome

First, we used demographic variables as above in order to discriminate the infants with a good outcome, bad outcome and the deaths[38]. Then another models was calculated with the morbidity and the therapeutic variables that were known during the stay of an infant.

Table 32: Statistic of variables used in discriminant analysis.

	Good outcome		Poor outcome		Deaths	
	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation
Gestational age	29.62	1.80	28.22	2.01	26.91	1.97
Birth weight	1305.60	344.15	1068.11	357.13	886.32	349.32
Head circumference	274.51	24.31	257.77	29.17	246.72	30.55
Umbilical artery pH	7.27	0.09	7.26	0.10	7.24	0.12
APGAR after 1 minute	6.15	2.25	5.16	2.47	3.82	2.32
APGAR after 5 minutes	8.11	1.46	7.54	1.77	6.34	2.06
APGAR after 10 minutes	8.75	1.13	8.26	1.37	7.70	1.58
Birth location	1.07	0.26	1.07	0.26	1.06	0.25
Gender	1.51	0.50	1.52	0.50	1.63	0.49
Mode of delivery	0.24	0.43	0.22	0.41	0.26	0.44
Multiple birth	0.68	0.47	0.77	0.42	0.73	0.45

Birth location (1=Inborn, 2=Outborn), Gender (1=Female, 2=Male), Mode of delivery (0=C-section, 1=Vaginal delivery), Multiple birth (0=Multiple birth, 1=Single birth)

The same 1081 data records were used for the first model; 799 with good outcome, 172 with poor outcome. The covariance matrices differed significantly between the three subgroups (Box's M 278.46, $p<0.0001$). The first discriminant function explained 95.7% of the variance and had a better discriminatory ability (Wilks'Lambda 0.74, $p<0.0001$) than the second one which wasn't significantly (Wilks'Lambda 0.99, $p=0.10$). The gestational age was the variable with the highest discriminatory power, followed by the APGAR score after 5 minutes (Table 33). The birth location was the one with the lowest power; other unimportant variables were head circumference, pH-value of the umbilical artery and the multiple birth. The scatter plot of the discriminant functions showed a high overlapping of the three subgroups, and therefore only 62% of the original data were classified correctly (Table 34). Instead using the

[38] Bahodo-Shing used a backward stepwise logistic regression analysis to determine the prenatally available variables to predict the overall outcome – defined as alive at discharge - and the survival without severe morbidity - defined as ROP stage 3-4, IVH grade 3-4, PVL, CLD and deafness – with infants below 1000g born between 1990 and 1995. The most significant variables for both models were the obstetric estimate of gestational age and the abdominal circumference. The estimated fetal birth weight wasn't significant.

observed group sizes instead equal prior probabilities as prior probabilities, 77% of the original data were classified correctly.

Table 33: The standardized canonical discriminant function coefficients.

Function coefficients	Discr. function 1	Discr. function 2
Gestational age	0.546	-0.064
Birth weight	0.304	-0.077
Head circumference	-0.016	0.514
Umbilical artery pH	0.042	0.076
APGAR after 1 minute	0.170	0.149
APGAR after 5 minutes	0.370	-1.245
APGAR after 10 minutes	-0.009	0.847
Birth location	-0.033	-0.028
Gender	-0.166	0.202
Mode of delivery	-0.075	0.297
Multiple birth	0.025	-0.431

Table 34: Classification result of the discriminant function as in Table with the original data and the equal (observed group size) prior probability.

	Neonatal outcome	Predicted Group Membership			Total
		Good outcome	Poor outcome	Death	
Count	Good outcome	533 (771)	176 (10)	90 (18)	799
	Poor outcome	61 (144)	60 (6)	51 (22)	172
	Death	12 (57)	26 (3)	72 (50)	110
%	Good outcome	66.7 (96.5)	22.0 (1.3)	11.3 (2.3)	100.00
	Poor outcome	35.5 (83.7)	34.9 (3.5)	29.7 (12.8)	100.00
	Death	10.9 (51.8)	23.6 (2.7)	65.5 (45.5)	100.00

Adding the other morbidity variables known at birth, that means congenital malformation and respiratory distress, 1081 infants born in the perinatal centres were used for the model specification – 799 with good outcome, 172 with poor outcome and 110 deaths. The covariance matrix was significantly different (Box's M 567.29, $p<0.0001$). As in the previous model, the first discriminant function explained 95.1% of the variance and had a better discriminatory ability (Wilks'Lambda 0.72, $p<0.0001$) than the second one which wasn't significantly (Wilks'Lambda 0.98, $p=0.08$). The discriminatory power of the variables didn't change compared to the above model. The gestational age and the APGAR score after 5 minutes had a high power. The birth location, the head circumference, pH-value of the umbilical artery, the multiple birth and the APGAR score after 10 minutes had a low power. Also the classification of the infants didn't differ essentially. 68% of the infants with a good outcome, 35% of the ones with a poor outcome and 64% of the deaths were specified correctly.

The third model consisted of all variables "representing" the dimension of all variables[39] - 920 data records whereby 707 infants with a good outcome, 129 with a poor outcome and 84 deaths. The Box's M of 646.5 indicated a significant difference of the covariance matrices

[39] Using all variables, the Wilks'Lambda didn't change much and the amount of overall correct specified data was 93.8% with 96.6% correct specified infants with a good outcome, 86.8% correct specified children with a bad outcome and 81.5% correct specified deaths. 12.3% of the deaths were misleading specified as infants with a good outcome. Also the variables with the highest and lowest discriminatory power didn't differ essentially. However by contemplating only the demographic variables, the power of the head circumference was astonishingly better than the one of the gestational age respective birth weight.

between the three subgroups (p<0.0001). The first discriminant function had a Wilks'Lambda 0.08 and the one of the second function amounted to 0.58; both a little less than in the previous model. Both functions were significantly (p<0.0001). The intracranial haemorrhage grade 3-4 and the cystic PVL and especially the BPD were the variables with the highest discriminatory power (Table 35). The variables with the lowest power were the therapies antenatal steroids and surfactant and the demographic variable the birth location, followed by the mode of delivery and the gender. Out of the therapy variables, the surgery had astonishingly the best discriminatory power. The scatter plot of the discriminant functions showed a low overlapping of the three subgroups. The amount of correct specified data was therefore 93.7% -94.0% with observed group sizes as prior probabilities (Table 36).

Table 35: The standardized canonical discriminant function coefficients.

Function coefficients	Discr. function 1	Discr. function 2	Function coefficients	Discr. function 1	Discr. function 2
Gestational age	-0.072	0.663	Intracran. haemorrhage grade 3-4	0.747	-0.220
Umbilical artery pH	-0.055	0.059	PVL	0.482	-0.033
APGAR after 1 minute	0.055	0.164	NEC	0.051	-0.179
APGAR after 5 minutes	-0.046	0.112	Sepsis	0.048	0.076
Birth location	0.009	-0.086	CLD	-0.030	0.516
Gender	-0.021	-0.092	BPD	1.248	0.083
Mode of delivery	0.030	0.014	RDS	0.051	-0.285
Multiple birth	0.028	0.047	Mechanical ventilation	0.045	-0.160
SGA	-0.015	-0.157	CPAP treatment	-0.020	0.531
SHC	0.078	-0.194	Surfactant	0.015	-0.027
Congenital malformation	0.070	-0.198	Antenatal steroids	0.010	-0.085
PDA	0.020	-0.112	Surgery	-0.109	-0.221

Table 36: Classification result of the discriminant function as in Table with the original data and the equal (observed group size) prior probability.

	Neonatal outcome	Predicted Group Membership			Total
		Good outcome	Poor outcome	Death	
Count	Good outcome	682 (699)	0 (0)	25 (8)	707
	Poor outcome	4 (7)	112 (111)	13 (11)	129
	Death	11 (24)	5 (5)	68 (55)	84
%	Good outcome	96.5 (98.9)	0 (0)	3.5 (1.1)	100.00
	Poor outcome	3.1 (5.4)	86.8 (86.0)	10.1 (8.5)	100.00
	Death	13.1 (28.6)	5.9 (5.9)	81.0 (65.5)	100.00

As for the discriminant model for the survivors /deaths, the more variables entered the model the better was the discriminatory power of the functions and the more infants were specified correctly into the groups of children with a good outcome, poor outcome and the deaths. In most of the models, the amount of correct specifications corresponded to the size of the three groups. However, using the group sizes as prior probability leaded to a non-acceptable result for the group of poor outcome and the deaths.

5 Discussion

5.1 Trends between 1996 and 2004

The identification of a temporal trend of the MNDS variables was one of the interests of this retrospective study. The rate of very low birth infants who were born alive in a perinatal centre increased from 7.6‰ to 9.0‰ over the eight years. An increasing frequency of high-risk births was also reported in the USA [40]. Most of the variables showed a stable level over time. A significant linear trend could only be found for a few. The incidence of multiple births increased significantly from 23% in 1996 to 31% in 2004 ($p_C<0.01$) and the one of inborns from 87% to 94% ($p_C<0.0001$).

The mortality rate of very preterm infants remained stable in Switzerland between 1996 and 2004 (on average 13%). The infants tended to die less frequently by increasing gestational age. The detail analysis showed a significant trend for the mortality rate of some variables. Infants with a major congenital malformation had a significant linear increase of their mortality rate over the years (14% in 1996, 42% in 2004; $p_C=0.03$). The mortality rate tended to increase linearly for the infants with a proven NEC (14% in 1996, 39% in 2004) or an intracranial haemorrhage grade 3-4 (from 52% to 62.5%). The children with a BPD tended to die less frequently over the years (6.8% in 1996, 1.2% in 2004).
The yearly change in the mortality rate was significantly for some therapies, although no linear trend could be found. The one of the infants with no surfactant (between 4.7% and 9.0%; $p_C<0.05$), with no mechanical ventilation (between 1.5% and 7.1%; $p_C<0.01$) and with only CPAP treatment (between 1.1% and 6.3%; $p_C=0.01$) changed significantly. The mortality rate of the infants with no CPAP administration increased significantly from 19.5% in 1996 to 34.1% in 2004 ($p_C<0.01$).

The frequency of infants with a PDA (from 17% to 23%; $p_C<0.05$) or a RDS (from 81% to 87%; $p_C<0.01$) increased significantly and linearly over the eight years. Also a significant change, but no linear increase could be found for the incidence of CLD. The rate of major malformations changed significantly over the years with a decreasing tendency between 1996 and 2004. No significant increase, but a tendency of a linear increase was observed for the incidence of intracranial haemorrhage grade 3-4 (from 7% to 9%) and for the ventricular dilatation >97th percentile. Platt [76] could show that the incidence of cerebral palsy decreased in 16 European centres in the period 1980-1996.
For the survivors, the rate of ROP grade 1-3 or grade 3 only remained stable over the years. Also the incidence of a poor outcome, defined as intracranial haemorrhage grade 3-4, cystic periventricular leucomalacia, ROP stage 3-4 or BPD, didn't change significantly (on average 19% of the survivors). The length of hospitalisation stay tended to decrease from 67 days in 1996 to 65 days in 2004, however not significantly. Catlin [41] argued that a very long hospitalisation stay is caused especially by a very prematurity, RDS and NEC in the USA. The decreasing duration of hospital stay might reduce the health cost per infant. Another possibility for a cost-reduction – Phipps and Schmitt could demonstrate it for California [56] – is the use of interventions that can delay or prevent preterm delivery unless they are very expensive.

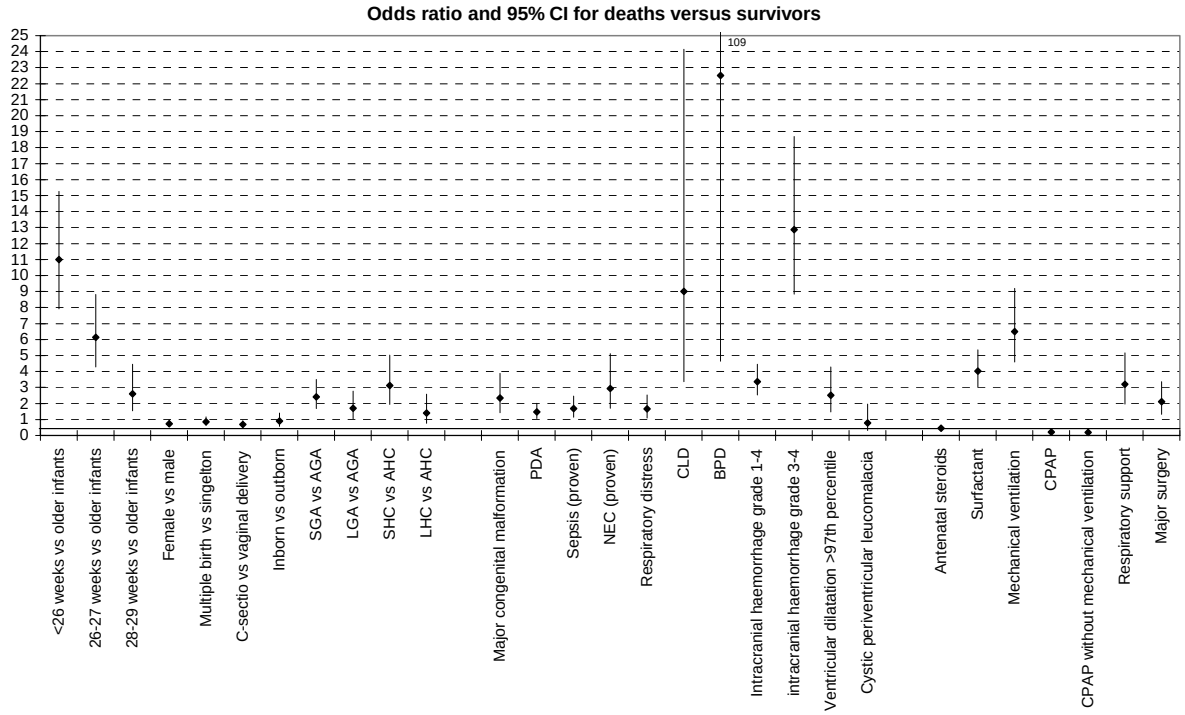
Antenatal steroids were given significantly more frequently ($p_C<0.0001$) in 2004 (76% of the infants) than in 2000 (64%). A highly significant linear increase ($p_C<0.01$) could be observed for the application of surfactant (33% in 2000, 39% in 2004). Also the infants were ventilated significantly more frequently ($p_C<0.0001$) with CPAP treatment (48% in 1996, 80% in 2004)

or only CPAP treatment (42% versus 22%) over the eight years. Opposite to that, the rate of mechanical ventilation decreased, however the rate changes weren't continuous. Adding together the two ventilation types, the respiratory support increased linearly and significantly (p_C<0.0001) from 74% in 1996 to 88% in 2004. A linear increasing, not-significant tendency was found for the application of major surgery.
Like for the frequency of ventilation, the same result could be observed for the duration of the ventilations. The duration of the mechanical ventilation decreased significantly (6.9 days in 2004 versus 8.6 days in 1996) and the one of the CPAP treatment (16.9 days versus 10.2 days) and respiratory support (19.8 days versus 13.2 days) increased significantly over the eight years. The duration of only the CPAP administration increased as well, however not significantly.

5.2 The short-term outcome

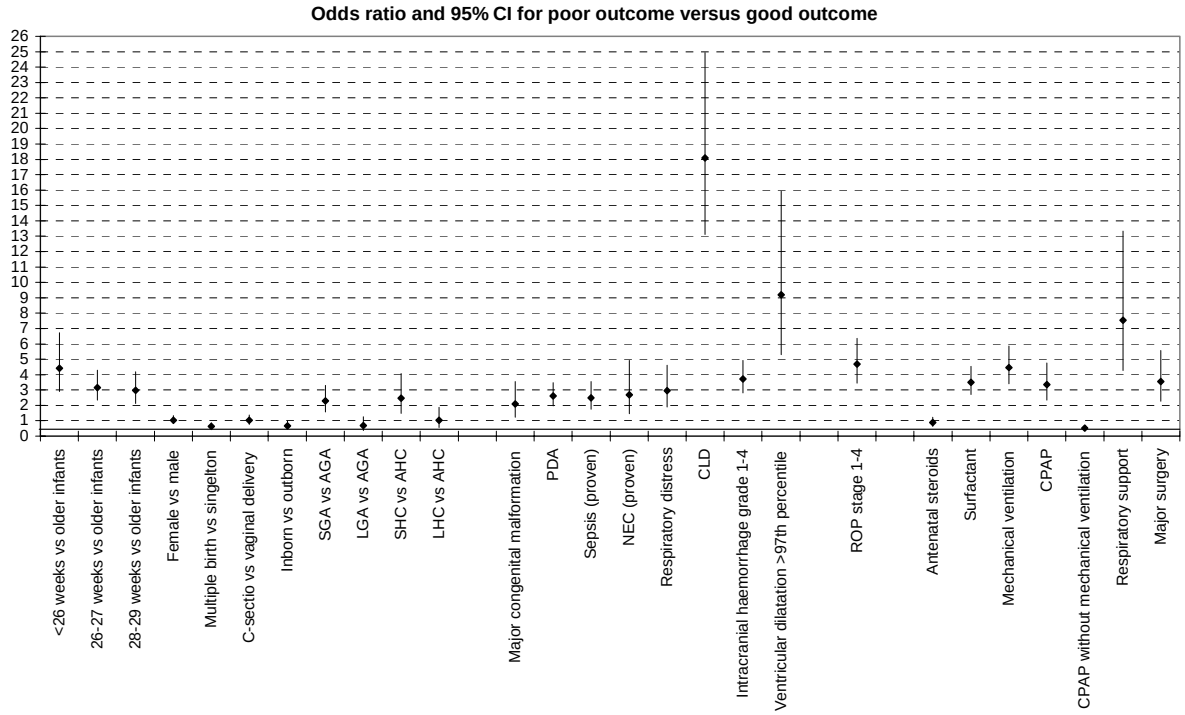
The analysis of the demographics revealed that significant more children with <26 completed gestational weeks were born by C-section (p_C<0.0001) or were small for their gestational age (p_C<0.01) compared to the older ones. Significantly less multiple births were observed for age 26-27 (p_C=0.04) respective 28-29 (p_C<0.0001) completed weeks than for the older ones. For the children with 26-27 completed weeks, significantly more infants were inborns (p_C=0.02), SGA ones (p_C<0.0001) or born by C-section (p_C=0.05).
Multiple births had significantly more frequently a C-section (OR 2.1-3.6; p_C<0.0001) or were born in a perinatal centre (OR 1.1-2.2; p_C=0.03), but they were significantly less often small (p_C=0.01) or large (p_C<0.001) for their gestational age. C-section was also done more frequently in the perinatal centres (OR 1.4-2.7; p_C<0.0001). SGA infants had significantly more often a C-section (OR 2.7-8.1; p_C<0.0001), on the other hand LGA ones a vaginal delivery (OR 1.4-3.0; p_C<0.001). The first group were born significantly more frequently in a perinatal centre (OR 1.5-7.2; p_C<0.01), the latter not significantly.

Figure 46: The odds ratio and its 95% confidence interval for deaths versus survivors



The mortality rate of very preterm infants amounted to 12.9% (95% CI 11.4%-14.4%) in the years 1996-2004. The neonatal deaths, defined as death within the first 28 days, were 11.5% (10.1%-12.9%). The gestational age was a significant factor (Figure 46). The infants with <26 completed gestational weeks died 11 times (OR 95% CI 7.9-15.3), the ones with 26-27 weeks 6 times (OR 95% CI 4.3-8.8) and the ones with 28-29 weeks almost 3 times (OR 95% CI 1.5-4.5) more frequently than the older children. Females (p_C=0.04) and C-section (p_C=0.01) was associated with a lower mortality rate. SGA (p_C<0.0001) and LGA children (p_C=0.03) had a higher mortality rate than the AGA ones. SGA infants have also a higher mortality rate during the first year of lifetheir childhood due to congenital malformation, perinatal asphyxia and transitional cardiorespiratory disorders [73].
All the examined morbidities except cystic PVL were associated with a significant higher mortality. The severe lung diseases CLD (OR 95% CI 3.4-24.1) and BPD (OR 95% CI 4.7-109.1) and IVH grade 3-4 (OR 95% CI 8.9-18.7) were the ones with the highest mortality. NEC was also one of the more lethal factors (OR 95% CI 1.7-5.1).
The very preterm infants who received antenatal steroids had a significant lower mortality rate (p_C<0.0001), on the other hand the surfactant couldn't improve the overall mortality rate (OR 95% CI 3.0-5.4), neither for the children with RDS (OR 95% CI 2.8-5.2). Giving surfactant didn't have any significant effect on the mortality rate of the infants with CLD or BPD. The mechanical ventilated children had a significant higher overall mortality rate as well (OR 95% CI 4.6-9.2); also the ones with RDS (OR 95% CI 4.4-9.6) or with CLD (OR 95% CI 1.2-67.1). Using CPAP treatment was associated with a significant lower overall mortality rate (OR 95% CI 0.2-0.3); the same result was valid for the infants with RDS (p_C<0.0001), CLD (p_C<0.001) or BPD (p_C<0.001).The infants with respiratory support had overall a significant higher mortality rate (OR 95% CI 2.0-5.2). Also the infants who had a major surgery had a significant higher risk of death (OR 95% CI 1.3-3.4).

Figure 47: The odds ratio and its 95% confidence interval for infants with a poor outcome versus the ones with a well outcome



The gestational age was negative correlated (Figure 47) with a good outcome defined as survivor without intracranial haemorrhage grade 3-4, cystic periventricular leucomalacia,

ROP stage 3-4 or BPD. The infants with <26 completed gestational weeks had a 4 times (OR 95% CI 2.9-6.7), the ones with 26-27 completed weeks a 3.2 times (OR 95% CI 2.3-4.3) and the ones with 28-29 completed weeks a 3.0 times (OR 95% CI 2.1-4.2) higher risk of a poor outcome than the older infants. Also the small for gestational age children were associated with a poor outcome (OR 95% CI 1.6-3.3). Only the multiple birth (p_C<0.01) and the inborns (p_C=0.04) had a significant lower incidence of a poor outcome. The mode of delivery didn't have an effect on the outcome – Drife got an analogous result [44], he could only show that only the mother with an infant <28 completed weeks born by an elective C-section had more likely serious morbidity. The result of the multiple births might be contradictory to the one of Hajnal [37] who couldn't find a significant different outcome, measured by a neurologic examination for the Swiss VLBW multiple births in the 1990s.
All other morbidities excluded in the definition of a poor outcome were associated with a significant lower incidence of good outcome. The infants with CLD (OR 95% CI 13.1-25.0) and a ventricular dilatation >97th percentile (OR 95% CI 5.3-15.9) had the highest risk of a poor outcome. The odds ratios of the other morbidities were between two and three. The survivors with ROP stage 1-3 had a 4.7 times higher incidence (OR 95% CI 3.5-6.4).
Most of the interventions were associated with a higher incidence of a poor outcome as well. The antenatal steroid was the only exception. The infants who got CPAP treatment only had a significant lower risk of a poor outcome (OR 95% CI 0.4-0.7). All other interventions didn't reduce the risk significantly. The children with surfactant had a 3.5 times (OR 95% CI 2.7-4.5), the mechanical ventilated ones a 4.5 times (OR 95% CI 3.4-5.9), the CPAP treated ones a 3.3 times (OR 95% CI 2.4-4.8), the ones with a major surgery a 3.5 times (OR 95% CI 2.3-5.6) higher risk than the infants without a therapy. The highest odds ratio of 7.6 had the children who received respiratory support (OR 95% CI 4.3-13.3).

The multiple births were born significantly more by C-section (OR 95% CI 2.1-3.7) and as inborns (OR 95% CI 1.1-2.2). They were significantly less often small (OR 95% CI 0.5-0.9) and large (OR 95% CI 0.3-0.7) for gestational age.
None of the different mortality rates differed significantly between single and multiple births. Major congenital observations were observed significantly less frequently for multiple births (OR 95% CI 0.3-0.8), also BPD (OR 95% CI 0.5-0.9). The surviving multiple births had significantly less frequently a ROP stage 3 (OR 95% CI 0.01-0.8). For the other morbidity entities, no significant differences were found. A good outcome were found significantly more frequently for the survivors (OR 95% CI 1.2-2.1).
Antenatal steroids were given to multiple births significantly more frequently (OR 95% CI 1.6-2.8). The multiple births had significantly less mechanical ventilation (OR 95% CI 0.6-1.0).

A C-section was applied more frequently to inborns (OR 95% CI 1.4-2.2) and to SGA infants (OR 95% CI 2.7-8.1), however not to LGA children (OR 95% CI 0.3-0.7).
As mentioned above, infants died significantly less often during their hospital stay when they were delivered by C-section (OR 95% CI 0.5-0.9). The lower early mortality rate was associated with C-section (OR 95% CI 0.5-1.0). Intracranial haemorrhage grade 1-4 and grade 3-4 were the only examined morbidities who occurred significantly less frequently for infants delivered by C-section (OR 95% CI 0.5-0.8 respective 0.5-1.0). For the survivors with C-section, the ROP stage 3 was found less often (OR 95% CI 0.1-0.7).
The children born by C-section had significantly more frequently antenatal steroids and surfactant (OR 95% CI 1.1-1.8 for both), and CPAP treatment as well (OR 95% CI 1.3-2.0).

Small gestational age children were born significantly more often by C-section (OR 95% CI 2.7-8.1) and as inborn (OR 95% CI 1.5-7.2)., They died significantly more frequently than

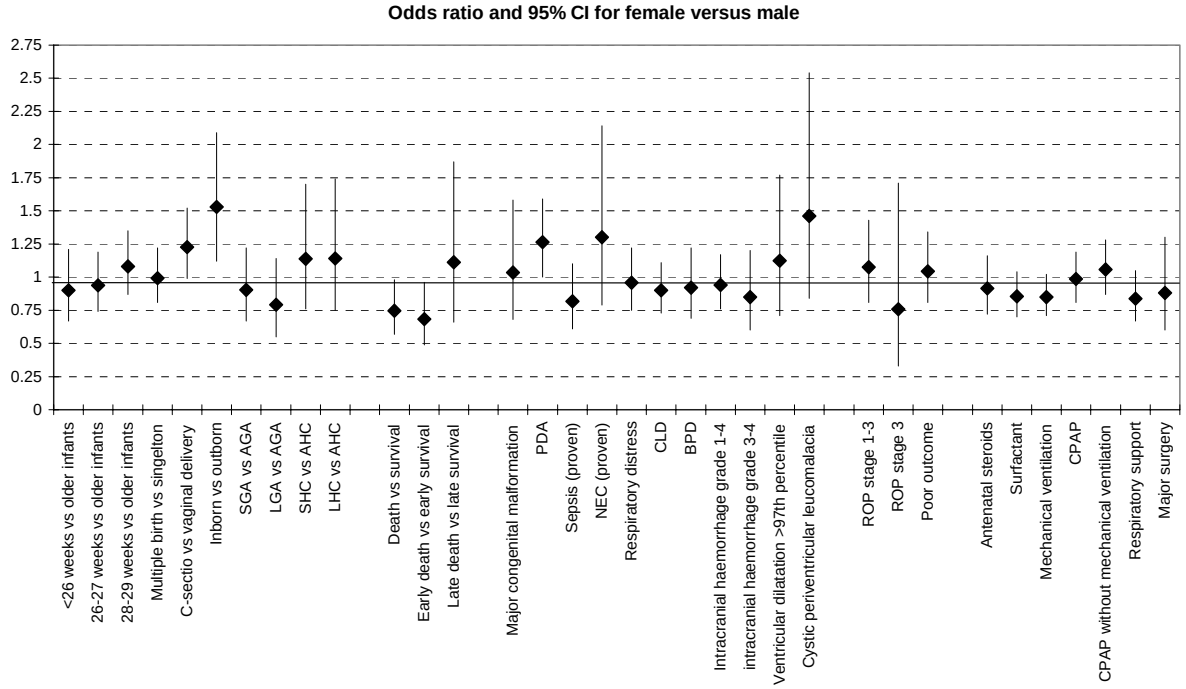
appropriate ones (OR 95% CI 1.7-3.5) during their hospital stay. Also the early and late mortality was significantly higher. The lung diseases CLD (OR 95% CI 1.8-5.4) and BPD (OR 95% CI 2.1-5.3) were associated with a small weight. SGA infants had significantly less frequently an intracranial haemorrhage grade 1-4 (OR 95% CI 0.5-1.0). None of the interventions were associated with a too small weight.

For the survivors, the average hospitalisation stay amounted to 65.8 days (95% CI 64.2-67.4 days). The gestational age was associated with a lower LOS: the survivors with <26 completed weeks were 113 days in the hospital (95% CI 105-121 days), the ones with 26-27 weeks 92 days (95% CI 88-95 days), the ones with 28-29 weeks 70 days (95% CI 67-72 days) and the children with 30-31 weeks 49 days (95% CI 47-50 days). The multiple births stayed significantly shorter in the hospital (p_C=0.02) than the singletons. The survivors with C-section had a significant longer stay than the vaginal delivered ones (p_C=0.04). Also the length of stay of the surviving SGA infants was significantly longer than the one of the AGA ones (p_C<0.0001).

5.3 Gender

The demographics showed no significant differences between females and males except for inborns (Figure 48). Significantly more females were inborns than outborns (OR 1.5, 95% CI 1.1-2.1). A trend, that wasn't significantly at all, could lead to the assumption that the gestational age was negatively correlated with a male sex.

Figure 48: The odds ratio and its 95% confidence interval for female versus male.



The female sex had a weak significant overall better survival rate than the males (p_C=0.04). Females died less frequently in the early neonatal period than males (OR 0.7, 95% CI 0.5-1.0). In the late neonatal period, no significant difference between the mortality rates could be found, although the females tended to die more frequently.

The gender wasn't associated with the incidence of the major morbidities except for the PDA. Significantly more females had a PDA than males (p_C=0.046). For most of the other morbidities, the female sex tended to have a lower risk. Exceptions were major congenital malformations, proven NEC, ventricular dilatation >97th percentile and cystic PVL.
Also for the survivors, the gender didn't differ in its incidence of poor respective good outcome. The length of stay didn't differ, too.

The use of intervention wasn't associated with the gender. No significant differences were found for all examined therapies, although the females tended to get them less frequently with the CPAP treatment without mechanical ventilation as the only exception.

A study that examined the long-term outcome of females versus males could find a difference in neurodevelopment outcomes, measured as neurodevelopmental impairment (NDI) or Bayley Mental Development Index (MDI) - boys were an independent risk factor for an adverse outcome - although the reason is unknown [48].

5.4 International studies

The Models of Organizing Access to Intensive care for Very Preterm Births (MOSAIC) study is the most important lately published international study because of geographic and socioeconomic closeness to Switzerland. The data were collected in 2003 in ten European region and were compared to the Swiss data of 2004. The in-hospital mortality rate didn't differ significantly between Swiss very preterm infants and all European infants (11.4% and 14.2%, respectively). Only single countries had a different mortality rate: The infants in the German region Hesse died less frequently (7.9%), the ones in the Belgium region Flanders (16.0%), in the Italian region Lazio (17.6%) and the ones in the Poland region died more frequently than in Switzerland.
The incidence of neurologic morbidity, defined as intraventricular haemorrhage grade 3-4 or cystic periventricular leucomalacia, didn't differ significantly either between the survivors in Switzerland and in the European region (5.9% and 7.4, respectively). Only the eastern region of Denmark had a significant lower rate (2.6%). Again the Belgium, Italian and Poland region had a significant higher incidence of neurologic morbidity (9.3%, 11.8% and 15.7%, respectively).
The survivors had a similar rate of bronchopulmonary dysplasia in Switzerland and the European region (14.9% and 15.8%, respectively). Significantly lower incidences were reported in Lazio (9.5%) and the eastern region of Denmark (10.3%). Both region in the United Kingdom - the northern region and Trent – had a significant higher incidence (25.2% and 21.2%, respectively).

Older international studies didn't show a consistent difference between Swiss very preterm infants and the ones in other countries, partly because of different definitions for the morbidities. The incidence of a sepsis was significantly lower in Switzerland in 1996 (9.6%) than in Netherlands in 1996-97 (27.1%) or in New Zealand in 1996 (26.2%). The same studies showed that the rate of Necrotising enterocolitis was significantly higher in Netherlands (9.4%) than in Switzerland (3.8%) and New Zealand (3.3%). The respiratory distress was significantly less frequently observed in Netherlands (58.6%) than in Switzerland (80.8%). The incidence of intraventricular haemorrhage grade 3-4 was equivalent in Netherlands and Switzerland (7.5% and 7.3%, respectively), however significantly higher than in New Zealand (4.8%). On the other hand, the rate of cystic periventricular leucomalacia was significantly higher in the latter than in Switzerland (12.6% and 3.0%, respectively).

In the examined years, surfactant and antenatal steroids were given less frequently in Switzerland than in Netherlands. A possible explanation is that Swiss perinatal centres didn't have much experience with these therapies because this gap was closed in the following years. The Swiss very preterm infants weren't mechanical ventilated as often as the ones in Netherlands or New Zealand.

Studies with birth weight as inclusion criteria had an analogues result in 1996 and 2000. Sepsis was significantly lower in Switzerland (on average 12%) than in Portugal (32%) and Finland (27%). The incidence of Necrotising enterocolitis was significantly lower in Switzerland (4%) than in Portugal (11%), Finland (9%), Canada (7%), USA (7%) and the Vermont Network (7%) – including 39 countries inclusive Switzerland. The rate of bronchopulmonary dysplasia was significantly higher in Portugal (23%), Finland (39%) and the USA 22%) than in Switzerland (14%). The Swiss very preterm infants had an intraventricular haemorrhage grade 3-4 as often (7%) as the ones in Canada (10%) or the Vermont Network (8%), however a significantly lower incidence than in Finland (17%).
In all these countries, surfactant and antenatal steroids were given more frequently in 2000 than in 1996. The very preterm infants had an increasing application of CPAP treatment and were less often mechanical ventilated over the period.

5.5 Mathematical models

Linear prediction models for the gestational age at dismission had a low explanation power that increased with the number of variables entering the model. The most extensive model used as significant variables with a positive coefficient congenital malformation, the proven sepsis, the BPD, the intracranial haemorrhage grade 3-4, the mechanical ventilation and the major surgery. The significant variables with a negative coefficient were the demographics – the head circumference, the information about multiple births and the APGAR score after 1 minute. The gestational age at birth wasn't significantly if several variables entered the model.

Using a factor model to determine redundant information of the variables, the results were disappointing: only the variable group gestational age, birth weight and head circumference had an obvious redundancy and also the group of the APGAR score after 1, 5 and 10 minutes. All other variables had to enter a model to improve the explanation power.

A discriminant model for survival respective death – using only the variables gestational age, birth weight, head circumference, pH-value of the umbilical artery, birth location, gender, mode of delivery, multiple birth and all three APGAR scores – had a sensitivity of 77% and a specificity of 78%. Using all variables, the sensitivity increased to 85% and the specificity to 93%.
Constructing a discriminant model for the outcomes with the same variable groups, 62% of the data were specified correctly with the smaller group, mainly the infants with a good outcome or death, however a poor outcome was specified in only 4% of the cases. A model using all variables specified correctly 94% of the data and the poor outcome was correctly predicted in 87%.

6 Appendix

6.1 Abbreviations

AGA	Appropriate for gestational age, birth weight ≥10th and <90th percentile of population based birth weight curve
AHC	Appropriate for head circumference, head circumference ≥10th and <90th percentile of population based head circumference curve
BfS	Swiss Federal Statistical Office
BPD	Bronchopulmonary dysplasia: a requirement for supplemental oxygen at 36 weeks postmenstrual age
BW	Birth weight
CI	Confidence interval
CLD	Chronic lung disease: a requirement for supplemental oxygen at day 28
CPAP	Continuous positive airway pressure
FRC	Functional residual capacity (of the lung)
GA	Gestational age
IVH	Intraventricular haemorrhage (Classification of Papile grade >1)
LGA	Large for gestational age, birth weight ≥90th percentile of population based birth weight curve
LHC	Large for head circumference, head circumference ≥90th percentile of population based head circumference curve
LOS	Length of stay
MNDS	Minimal neonatal data set
n.a.	not available
NEC	Necrotising enterocolitis
NEO	Swiss Society of Neonatology
NICU	Neonatal intensive care unit
NPV	Negative predictive value
n.s.	not significant
OR	Odds ratio
p_C	Pearson Chi-square p-value
p_L	Linear-by-linear association p-value
PDA	Persistent ductus arteriosus
PMA	Postmenstrual age
PPV	Positive predictive value
PVL	Periventricular leucomalacia
RDS	Hyaline membrane disease (in UK/US: respiratory distress syndrome)
ROP	Retinopathia praematurorum
SGA	Small for gestational age, birth weight <10th percentile of population based birth weight curve
SHC	Small for head circumference, head circumference <10th percentile of population based head circumference curve
SSW	Completed gestational weeks
VLBW	Very low birth weight i.e. birth weight <1500g

6.2 Tables

Table 37: Number of infants in the MNDS and delivered to the perinatal centres

	Population		1996		2000		2004	
	n	%	n	%	n	%	n	%
Infants reported to MNDS	1934		606		674		654	
Infants died in delivery room	63	3.3	18	3.0	21	3.1	24	3.7
Infants delivered to perinatal centres	1848		573		645		630	

Table 38: Number of infants in each gestational age group

Gestational age	Population		1996		2000		2004	
(completed weeks)	n	% per year	n	% per year	n	% per year	n	% per year
23	6	0.3%	0	0.0%	3	0.5%	3	0.5%
24	44	2.4%	8	1.4%	18	2.8%	18	2.9%
25	147	8.0%	48	8.4%	55	8.5%	44	7.0%
26	143	7.7%	36	6.3%	52	8.1%	55	8.7%
27	203	11.0%	57	9.9%	77	11.9%	69	11.0%
28	251	13.6%	86	15.0%	87	13.5%	78	12.4%
29	260	14.1%	81	14.1%	86	13.3%	93	14.8%
30	357	19.3%	113	19.7%	126	19.5%	118	18.7%
31	437	23.6%	144	25.1%	141	21.9%	152	24.1%
Infants delivered to perinatal centres	1848	100.0%	573	100.0%	645	100.0%	630	100.0%

Table 39: Statistics of all infants of the perinatal centres

	Population			1996		2000		2004		Pearson Chi-square	Linear-by-Linear-Association
	n	%	(95% CI)	n	%	n	%	n	%		
Mean GA	29.1			29.2		28.9		29.1			
(25th quantile, 75th quantile)	(27.4,30.9)			(27.7,31.0)		(27.3,30.9)		(27.4,30.9)			
Mean BW	1219			1235		1206		1217			
(25th quantile, 75th quantile)	(920,1500)			(930,1520)		(910,1480)		(920,1500)			
Mean head circumference	268					268		268			
(25th quantile, 75th quantile)	(250,285)			n.a.		(250,288)		(250,285)			
Mean pH-value of umbilical artery (25th	7.26					7.25		7.28			
quantile, 75th quantile)	(7.23,7.33)			n.a.		(7.21,7.32)		(7.24,7.33)			
Female	878	47.5	(45.2,49.8)	267	46.6	316	49.0	295	46.8	0.6446	0.9577
Multiple birth	515	27.9	(25.8,29.9)	132	23.0	185	28.7	198	31.4	0.0044	0.0013
Caesarean section	1369	74.6	(72.6,76.6)	408	71.2	483	76.2	478	76.1	0.0786	0.0547
Inborn	1660	89.9	(88.5,91.3)	498	86.9	568	88.3	594	94.3	3.1E-05	1.8E-05
SGA	197	10.7	(9.3,12.1)	54	9.4	68	10.5	75	11.9	0.3817	0.1661
AGA	1525	82.6	(80.8,84.3)	477	83.4	533	82.6	515	81.7	0.7530	0.4520
LGA	125	6.8	(5.6,7.9)	41	7.2	44	6.8	40	6.3	0.8509	0.5715
SHC	105	8.5	(7.0,10.1)	n.a.		50	8.2	55	8.9	0.6532	0.6531
AHC	1035	83.9	(81.9,86.0)	n.a.		507	82.7	528	85.2	0.2407	0.2406
LHC	93	7.5	(6.1,9.0)	n.a.		56	9.1	37	6.0	0.0352	0.0346
Infants delivered to perinatal centres	1848			573		645		630			

Table 40: Statistics and Odds ratio for female

	Population			1996		2000		2004		Odds ratio female versus. male		Pearson Chi-square	Linear-by-Linear-Association
	n	%	(95% CI)	n	%	n	%	n	%	OR	(95% CI)		
<26 completed weeks	89	45.2	(38.2,52.2)	24	42.9	37	48.7	28	43.1	0.90[a]	(0.67,1.21)	0.7353	0.9904
26-27 completed weeks	161	46.5	(41.2,51.8)	46	49.5	61	47.3	54	43.5	0.94[a]	(0.74,1.19)	0.6723	0.3795
28-29 completed weeks	252	49.3	(45,53.7)	81	48.5	87	50.3	84	49.1	1.08[a]	(0.87,1.35)	0.9454	0.9111
30-31 completed weeks	376	47.4	(43.9,50.8)	116	45.1	131	49.1	129	47.8	0.99[b]	(0.82,1.19)	0.6572	0.5506
Multiple birth	244	47.4	(43.1,51.7)	63	47.7	96	51.9	85	42.9	0.99	(0.81,1.22)	0.2133	0.3010
Singleton	634	47.6	(44.9,50.2)	204	46.3	220	47.8	210	48.6			0.7773	0.4861
Caesarean section	669	48.9	(46.2,51.5)	199	48.8	235	48.7	235	49.2	1.23	(0.99,1.52)	0.9866	0.9039
Vaginal delivery	204	43.8	(39.3,48.3)	68	41.2	76	50.3	60	40.0			0.1391	0.8707
Inborn	806	48.6	(46.1,51.0)	242	48.6	283	49.8	281	47.3	1.53	(1.12,2.09)	0.6917	0.6441
Outborn	71	61.8	(31.1,45.2)	25	33.3	32	42.7	14	38.9			0.4981	0.4313
SGA	90	45.7	(38.7,52.7)	25	46.3	26	38.2	39	52.0	0.90[c]	(0.67,1.22)	0.2548	0.4333
AGA	735	48.2	(45.7,50.7)	224	47.0	274	51.4	237	46.0	1.16	(0.91,1.48)	0.1764	0.7355
LGA	53	42.4	(33.6,51.2)	18	43.9	16	36.4	19	47.5	0.79[c]	(0.55,1.14)	0.5711	0.7498
SHC	53	50.5	(40.8,60.2)	23	46.0	30	54.5	53	50.5	1.14[d]	(0.76,1.70)	0.3817	0.3840
AHC	489	47.2	(44.2,50.3)	247	48.7	242	45.8	489	47.2	0.88	(0.65,1.19)	0.3528	0.3530
LHC	47	50.5	(40.2,60.9)	30	53.6	17	45.9	47	50.5	1.14[d]	(0.75,1.74)	0.4716	0.4740

a: age group versus older infants
b: 30-31 completed weeks versus younger infants
c: SGA (respectively LGA) versus AGA
d: SHC (respectively LHC) versus AHC

Table 41: Mortality data for all infants delivered to the perinatal centres

	Population			1996		2000		2004		Odds ratio[a]		Pearson Chi-square	Linear-by-Linear-Association
	n	%	(95% CI)	n	%	n	%	n	%	OR	(95% CI)		
Early neonatal deaths	154	8.3	(7.1,9.5)	48	8.4	59	9.1	47	7.5			0.5517	0.5484
Late neonatal deaths	59	3.5	(2.6,4.3)	17	3.2	24	4.1	18	3.1			0.6008	0.8672
Neonatal deaths	213	11.5	(10.1,12.9)	65	11.3	83	12.9	65	10.3			0.3569	0.5529
GA <26 completed weeks	99	50.3	(36.7,50.6)	29	51.8	43	56.6	27	41.5	10.99	(7.91,15.27)	0.1975	0.2360
GA 26-27 completed weeks	79	22.8	(16.2,24.7)	22	23.7	30	23.3	27	21.8	6.14[b]	(4.28,8.81)	0.9381	0.7355
GA 28-29 completed weeks	37	7.2	(4.5,8.8)	12	7.2	13	7.5	12	7.0	2.62[b]	(1.54,4.46)	0.9838	0.9516
GA 30-31 completed weeks	23	2.9	(1.6,3.9)	8	3.1	9	3.4	6	2.2	0.12	(0.07,0.18)	0.7073	0.5372
Female	98	11.2	(9.1,13.2)	30	11.2	44	13.9	24	8.1	0.74	(0.57,0.98)	0.0759	0.2215
Male	140	14.4	(12.2,16.6)	41	13.4	51	15.5	48	14.3	1.34	(1.02,1.77)	0.7512	0.7517
Singleton	178	13.4	(11.5,15.1)	59	13.4	68	14.8	51	11.8	1.17	(0.86,1.60)	0.4259	0.4989
Multiple birth	60	11.7	(8.9,14.4)	12	9.1	27	14.6	21	10.6	0.86	(0.63,1.17)	0.2715	0.8200
Vaginal delivery	76	16.3	(12.9,19.6)	28	17.0	29	19.2	19	12.7	1.46	(1.09,1.97)	0.2954	0.3177
Caesarean section	161	11.8	(10.1,13.4)	43	10.5	65	13.5	53	11.1	0.68	(0.51,0.92)	0.3438	0.8535
Inborn	211	12.7	(11.1,14.3)	60	12.0	85	15.0	66	11.1	0.90	(0.58,1.39)	0.1244	0.5722
Outborn	26	14.0	(8.9,19.0)	11	14.7	9	12.0	6	16.7	1.12	(0.72,1.73)	0.7827	0.8981
SGA	46	23.4	(17.4,29.3)	8	14.8	21	30.9	17	22.7	2.43[c]	(1.68,3.50)	0.1123	0.3910
AGA	170	11.1	(9.6,12.7)	57	11.9	65	12.2	48	9.3	0.47	(0.34,0.64)	0.2676	0.1817
LGA	22	17.6	(10.8,24.3)	6	14.6	9	20.5	7	17.5	1.70[c]	(1.05,2.77)	0.7803	0.7325
SHC	28	26.7	(18.1,35.2)	n.a.		17	34.0	11	20.0	3.12[d]	(1.94,5.03)	0.1052	0.1069
AHC	108	10.4	(8.6,12.3)	n.a.		54	10.7	54	10.2	0.45	(0.30,0.66)	0.8237	0.8237
LHC	13	14.0	(6.8,21.1)	n.a.		10	17.9	3	8.1	1.39[d]	(0.75,2.59)	0.1845	0.1869
Infants delivered to perinatal centres	238	12.9	(11.4,14.4)	71	12.4	95	14.7	72	11.4			0.1950	0.5850

a: OR calculated for selected group against the rest (if not mentioned otherwise)
b: OR calculated for selected group against the older infants
c: OR calculated for selected group against AGA
d: OR calculated for selected group against AHC

Table 42: Morbidity data for all infants of the perinatal centres

	Population			1996		2000		2004		Odds ratio deaths versus survivors		Pearson Chi-square	Linear-by-Linear-Association
	n	%	(95% CI)	n	%	n	%	n	%	OR	(95% CI)		
Major congenital malformation	89	4.8	(3.8,5.8)	43	7.5	20	3.1	26	4.1	2.35	(1.42,3.88)	0.0010	0.0078
PDA	366	19.8	(18,21.6)	98	17.1	125	19.4	143	22.7	1.47	(1.07,2.02)	0.0491	0.0147
Sepsis (proven)	202	10.9	(9.5,12.4)	55	9.6	82	12.7	65	10.3	1.68	(1.14,2.46)	0.1834	0.7275
NEC (proven)	65	3.5	(2.7,4.4)	22	3.8	25	3.9	18	2.9	2.95	(1.7,5.13)	0.5410	0.3471
Respiratory distress	1538	83.2	(81.5,84.9)	463	80.8	524	81.2	551	87.5	1.67	(1.09,2.54)	0.0021	0.0017
CLD	515	31.5[a]	(29.2,33.8)	167	32.9[a]	152	27.0[a]	196	34.7[a]	9.01	(3.36,24.14)	0.0160	0.4676
BPD	223	13.8[b]	(12.1,15.5)	73	14.4[b]	66	12.0[b]	84	15.0[b]	22.52	(4.65,109.13)	0.3056	0.7435
Intracranial haemorrhage grade 1-4	444	25.1	(23.1,27.1)	133	23.2	179	27.8	132	24.0	3.36	(2.53,4.46)	0.1434	0.7558
intracranial haemorrhage grade 3-4	140	7.9	(6.7,9.2)	42	7.3	50	7.8	48	8.7	12.86	(8.85,18.69)	0.6797	0.3925
Ventricular dilatation >97th percentile	78	4.7	(3.7,5.7)	25	4.4	30	4.7	23	5.1	2.52	(1.48,4.28)	0.8411	0.5611
Cystic periventricular leucomalacia	53	3.1	(2.3,3.9)	17	3.0	15	2.3	21	4.1	0.77	(0.3,1.96)	0.2140	0.2929

a: as percentage of the infants who were alive on the 28th day
a: as percentage of the infants who were alive on the 36th postmenstrual week

Table 43: Morbidity data for all survivors of the perinatal centres

	Population			1996		2000		2004		Pearson Chi-square	Linear-by-Linear-Association
	n	%	(95% CI)	n	%	n	%	n	%		
ROP stage 1-3	222	13.8	(12.1,15.5)	63	12.5	74	13.5	85	15.2	0.4319	0.2031
ROP stage 3	24	1.5	(0.9,2.1)	11	2.2	4	0.7	9	1.6	0.1410	0.4722
Poor outcome	298	18.5	(16.6,20.4)	97	19.3	88	16.0	113	20.3	0.1622	0.6557
LOS (mean days)	65.8		(64.2,67.4)	67.3		65.2		65.0		0.4837	0.2437

Table 44: Odds ratios of the morbidity data for all infants of the perinatal centres

	<26 weeks versus older infants		26-27 weeks versus older infants		28-29 weeks versus older infants		Female versus male		Multiple birth versus singletons		C-section versus vaginal delivery	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Major congenital malformation	1.06	(0.54,2.09)	1.12	(0.65,1.92)	1.01	(0.60,1.71)	1.03	(0.68,1.58)	0.47	(0.26,0.84)	0.77	(0.48,1.23)
PDA	2.59	(2.32,4.01)	3.05	(2.32,4.01)	2.95	(2.13,4.08)	1.26	(1.00,1.59)	0.92	(0.71,1.19)	1.10	(0.84,1.43)
Sepsis (proven)	2.72	(1.87,3.95)	3.11	(2.21,4.37)	3.17	(2.03,4.94)	0.82	(0.61,1.10)	0.96	(0.69,1.34)	1.17	(0.83,1.66)
NEC (proven)	2.64	(1.45,4.79)	1.49	(0.79,2.79)	1.98	(1.02,3.86)	1.30	(0.79,2.14)	0.70	(0.39,1.28)	1.04	(0.59,1.85)
Respiratory distress	1.68	(1.06,2.67)	2.95	(1.95,4.48)	2.68	(1.96,3.68)	0.96	(0.75,1.22)	1.05	(0.80,1.38)	1.16	(0.88,1.53)
CLD	13.49	(8.05,22.63)	10.25	(7.63,13.76)	5.46	(3.99,7.48)	0.90	(0.73,1.11)	0.81	(0.64,1.03)	1.08	(0.85,1.38)
BPD	4.27	(2.76,6.59)	3.93	(2.83,5.47)	3.21	(2.14,4.82)	0.92	(0.69,1.22)	0.66	(0.47,0.93)	1.22	(0.86,1.71)
Intracranial haemorrhage grade 1-4	2.20	(1.61,3.02)	2.00	(1.53,2.61)	1.65	(1.25,2.17)	0.94	(0.76,1.17)	0.98	(0.77,1.25)	0.60	(0.48,0.77)
intracranial haemorrhage grade 3-4	3.54	(2.35,5.35)	3.56	(2.37,5.36)	4.65	(2.55,8.50)	0.85	(0.60,1.20)	0.94	(0.64,1.39)	0.65	(0.45,0.95)
Ventricular dilatation >97th percentile	1.65	(0.88,3.13)	2.20	(1.31,3.72)	3.51	(1.83,6.71)	1.12	(0.71,1.77)	0.85	(0.50,1.44)	0.63	(0.39,1.02)
Cystic periventricular leucomalacia	1.55	(0.72,3.34)	1.29	(0.65,2.58)	1.14	(0.57,2.28)	1.46	(0.84,2.54)	0.61	(0.30,1.22)	1.02	(0.54,1.93)

	Inborn versus outborn		SGA versus AGA		LGA versus AGA		SHC versus AHC		LHC versus AHC	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Major congenital malformation	0.88	(0.45,1.73)	1.37	(0.71,2.65)	2.93	(1.59,5.39)	1.96	(0.80,4.82)	2.64	(1.13,6.16)
PDA	1.03	(0.70,1.51)	1.14	(0.79,1.64)	0.92	(0.58,1.47)	1.48	(0.94,2.33)	1.20	(0.73,1.99)
Sepsis (proven)	1.16	(0.70,1.94)	1.21	(0.77,1.89)	0.96	(0.53,1.75)	0.98	(0.52,1.85)	1.13	(0.60,2.13)
NEC (proven)	0.60	(0.30,1.20)	1.74	(0.89,3.41)	0.98	(0.35,2.75)	3.65	(1.73,7.72)	1.16	(0.35,3.87)
Respiratory distress	0.91	(0.60,1.38)	1.04	(0.69,1.55)	0.89	(0.56,1.43)	1.01	(0.58,1.76)	1.35	(0.71,2.60)
CLD	0.75	(0.54,1.04)	2.11	(1.51,2.95)	0.69	(0.43,1.11)	2.17	(1.36,3.46)	0.74	(0.44,1.24)
BPD	0.63	(0.41,0.95)	3.11	(2.13,4.55)	0.53	(0.24,1.16)	3.37	(2.02,5.64)	0.92	(0.45,1.89)
Intracranial haemorrhage grade 1-4	0.76	(0.54,1.06)	0.68	(0.46,0.99)	0.81	(0.52,1.27)	0.88	(0.54,1.44)	1.25	(0.77,2.02)
intracranial haemorrhage grade 3-4	0.59	(0.36,0.96)	0.76	(0.41,1.41)	0.71	(0.32,1.55)	0.78	(0.33,1.84)	1.23	(0.57,2.63)
Ventricular dilatation >97th percentile	0.71	(0.37,1.37)	0.78	(0.35,1.73)	0.54	(0.17,1.74)	0.94	(0.33,2.68)	2.17	(0.98,4.81)
Cystic periventricular leucomalacia	0.75	(0.33,1.69)	0.32	(0.08,1.35)	1.35	(0.52,3.46)	n.a.		0.98	(0.30,3.28)

Table 45: Odds ratios of the morbidity data for survivors of the perinatal centres

	<26 weeks versus older infants		26-27 weeks versus older infants		28-29 weeks versus older infants		Female versus male		Multiple birth versus singletons		C-section versus. vaginal delivery	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
ROP stage 1-3	4.80	(3.11,7.40)	3.66	(2.62,5.12)	3.14	(2.10,4.69)	1.07	(0.81,1.43)	0.96	(0.70,1.31)	1.31	(0.92,1.85)
ROP stage 3	25.03	(10.8,58.03)	4.73	(1.36,16.47)	6.55	(0.73,58.81)	0.76	(0.33,1.71)	0.11	(0.01,0.81)	0.32	(0.14,0.71)
Poor outcome	4.42	(2.91,6.73)	3.16	(2.33,4.29)	2.99	(2.13,4.19)	1.04	(0.81,1.34)	0.64	(0.48,0.87)	1.03	(0.77,1.39)

	Inborn versus outborn		SGA versus AGA		LGA versus AGA		SHC versus AHC		LHC versus AHC	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
ROP stage 1-3	1.07	(0.66,1.73)	1.90	(1.26,2.87)	0.55	(0.26,1.15)	2.09	(1.22,3.60)	0.31	(0.11,0.87)
ROP stage 3	0.55	(0.18,1.62)	1.91	(0.64,5.70)	0.69	(0.09,5.20)	3.72	(1.00,13.8)	n.a.	
Poor outcome	0.68	(0.46,0.99)	2.29	(1.58,3.31)	0.69	(0.38,1.25)	2.46	(1.49,4.07)	1.02	(0.56,1.87)

Table 46: Therapy data for all infants of the perinatal centres

	Population			1996		2000		2004		Odds ratio deaths versus survivors		Pearson Chi-square	Linear-by-Linear-Association
	n	%	(95% CI)	n	%	n	%	n	%	OR	(95% CI)		
Antenatal steroids	891	69.9	(67.4,72.4)	n.a.		414	64.2	477	75.7	0.46	(0.33,0.64)	7.3E-06	6.8E-06
Surfactant	628	34.0	(31.8,36.1)	n.a.		212	32.9	244	38.7	4.04	(3.04,5.36)	0.0047	0.0014
Mechanical ventilation	869	47.0	(44.7,49.3)	298	52.0	277	42.9	294	46.7	6.50	(4.59,9.20)	0.0066	0.0750
CPAP treatment	1203	65.1	(62.9,67.3)	276	48.2	420	65.1	507	80.5	0.22	(0.17,0.30)	1.2E-30	8.6E-32
CPAP without mechanical ventilation	611	33.1	(30.9,35.2)	126	22.0	222	34.4	263	41.7	0.19	(0.12,0.29)	2.1E-12	4.3E-13
Respiratory support	1480	80.1	(78.3,81.9)	424	74.0	499	77.4	557	88.4	3.19	(1.97,5.17)	3.2E-10	2.8E-10
Major surgery	110	6.0	(4.9,7)	29	5.1	38	5.9	43	6.8	2.11	(1.32,3.36)	0.4328	0.1960

Table 47: Odds ratios of the therapy data for all infants of the perinatal centres

	<26 weeks versus older infants		26-27 weeks versus older infants		28-29 weeks versus older infants		Female versus male		Multiple birth versus singletons		C-section versus vaginal delivery	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Antenatal steroids	0.54	(0.38,0.77)	1.03	(0.76,1.41)	0.83	(0.61,1.11)	0.91	(0.72,1.16)	2.09	(1.57,2.77)	1.40	(1.06,1.84)
Surfactant	3.11	(2.30,4.21)	3.64	(2.85,4.66)	2.11	(1.63,2.72)	0.85	(0.70,1.04)	0.81	(0.65,1.01)	1.40	(1.11,1.76)
Mechanical ventilation	6.94	(4.69,10.25)	3.90	(3.03,5.03)	2.51	(1.99,3.17)	0.85	(0.71,1.02)	0.78	(0.63,0.95)	1.13	(0.92,1.40)
CPAP treatment	0.76	(0.56,1.03)	1.86	(1.42,2.43)	2.01	(1.58,2.55)	0.99	(0.81,1.19)	0.90	(0.73,1.11)	1.58	(1.27,1.96)
CPAP without mechanical ventilation	0.20	(0.13,0.33)	0.59	(0.45,0.76)	0.95	(0.76,1.20)	1.06	(0.87,1.28)	1.02	(0.82,1.27)	1.20	(0.96,1.51)
Respiratory support	4.24	(2.34,7.69)	6.79	(4.11,11.23)	3.23	(2.41,4.32)	0.84	(0.67,1.05)	0.71	(0.55,0.90)	1.52	(1.19,1.96)
Major surgery	1.06	(2.13,5.26)	2.08	(1.29,3.34)	1.78	(1.03,3.09)	0.88	(0.60,1.3)	0.83	(0.53,1.37)	0.89	(0.58,1.37)

	Inborn versus outborn		SGA versus AGA		LGA versus AGA		SHC versus. AHC		LHC versus AHC	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Antenatal steroids	3.33	(2.24,4.95)	0.79	(0.55,1.15)	0.53	(0.34,0.84)	0.96	(0.62,1.49)	0.64	(0.41,0.99)
Surfactant	0.68	(0.50,0.93)	0.99	(0.73,1.36)	1.27	(0.87,1.85)	1.08	(0.71,1.64)	1.21	(0.78,1.86)
Mechanical ventilation	0.58	(0.43,0.79)	0.92	(0.69,1.24)	1.03	(0.72,1.49)	0.99	(0.66,1.48)	1.01	(0.66,1.54)
CPAP treatment	1.30	(0.95,1.77)	1.26	(0.91,1.74)	0.55	(0.38,0.80)	1.28	(0.79,2.07)	0.92	(0.58,1.48)
CPAP without mechanical ventilation	1.43	(1.02,2.01)	1.35	(0.99,1.83)	0.77	(0.51,1.16)	1.22	(0.81,1.83)	0.98	(0.63,1.52)
Respiratory support	0.66	(0.43,1.01)	1.40	(0.93,2.11)	0.76	(0.50,1.17)	1.44	(0.79,2.63)	0.98	(0.56,1.72)
Major surgery	1.13	(0.58,2.20)	1.23	(0.69,2.21)	0.81	(0.35,1.90)	1.84	(0.93,3.61)	1.08	(0.46,2.57)

Table 48: Duration (mean days) of the therapies for all survivors of the perinatal centres (taken only the infants into account who received the therapy)

	Population		1996	2000	2004	Pearson Chi-square	Linear-by-Linear-Association
	days	(95% CI)	days	days	days		
Mechanical ventilation	7.8	(7.0,8.6)	8.6	7.9	6.9	0.0726	0.0811
CPAP treatment	14.7	(13.6,15.7)	10.2	14.9	16.9	0.2721	<0.0001
CPAP without mechanical ventilation	11.7	(10.5,12.9)	9.3	12.2	12.4	0.3617	0.1080
Respiratory support	17.2	(16.1,18.3)	13.2	17.6	19.8	0.6039	<0.0001

Table 49: Duration (mean days) of the therapies for all surviving males and females of the perinatal centres (included only the infants who received the therapy)

	Female					Male					Pearson Chi-square	Linear-by-Linear-Association
	Population		1996	2000	2004	Population		1996	2000	2004		
	days	(95% CI)	days	days	days	days	(95% CI)	days	days	days	for population	for population
nical ventilation	7.6	(6.4,8.7)	8.7	7.2	6.9	8.0	(6.9,9.0)	8.5	8.5	6.8	0.9500	0.6276
	14.9	(13.4,16.4)	9.8	14.3	18.0	14.4	(13,15.9)	10.5	15.5	15.9	0.3326	0.6828
without mechanical ventilation	11.1	(9.5,12.7)	9.3	10.7	12.4	12.3	(10.4,14.2)	9.4	13.8	12.3	0.2422	0.3532
atory support	17.3	(15.7,18.8)	12.6	16.6	21.1	17.1	(15.6,18.6)	13.6	18.6	18.6	0.4076	0.8948

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8 Acknowledgements

I am particularly grateful to Professor H.U. Bucher for his expert advice and helpful criticism of nuances of meaning of style. I would like to acknowledge also the efforts of the staff within the Swiss Neonatal Network & Follow-up Group listed below and the participating clinics for their help and assistance during the data collection and verification. I specially thank M. Adams for his support in data collection and verification. I also acknowledge PD Dr. M. Voigt from the university Rostock who was so kind to provide me with the percentile charts for preterm infants. I should like to thank my sister Gabriella Hegglin and Reto Podetti for their help with linguistics. For the mistakes that remain despite all advice, I accept full responsibility.
Last but not least, I am very grateful for the support of my family during the last years of the medical study.

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9 Curriculum vitae

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